Gait Asymmetry and the Risk of Knee Osteoarthritis in Post-Stroke Individuals

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Table of Contents

List of figures

List of tables

Author declaration

I declare that this PhD thesis has been composed by myself and embodies the results of my own course of study and research whilst studying at The University of Salford from July 2014 to May 2018. All sources and material have been acknowledged.

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Abbreviations

3D	Three-Dimensional
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ASIS	Anterior Superior Iliac Spine
Asym	Asymmetry
BASIC	Brain and Spinal Cord Injury Centre
BBS	Berg Balance Scale
BMI	Body Mass Index
BMD	Bone Mass Density
CAST	Calibrated Anatomical System Technique
CI	Confidence Interval
CMC	Correlation of Multiple Coefficient
CoM	Centre of Mass
DOF	Degrees-Of-Freedom
EMG	Electromyography
ECM	Extracellular Matrix
GRF	Ground Reaction Force
Hz	Hertz
ICC	Intra-class Correlation Coefficient
KAM	Knee Adduction Moment
KFM	Knee Flexion Moment
KFMC	King Fahad Medical City
kg	Kilogram
KL	Kellgren and Lawrence
KOOS	Knee Osteoarthritis Outcome Score
m	Meter
MRI	Magnetic resonance imaging
Nm	Newton meter
NP	Non-Paretic
OA	Osteoarthritis

P	Paretic
RoM	Range of Motion
s	second
SD	Standard Deviation
SEM	Standard Error of Measurement
Spat	Spatial
SPSS	Statistical Package for the Social Sciences
SS	Self-Selected
Sym	Symmetry
Temp	Temporal
THR	Total Hip Replacement
TUG	Time Up and Go
vGRF	vertical Ground-Reaction Force
WHO	World Health Organization

Abstract

Background: Gait impairments, including asymmetry of walking, are common following a stroke and unfortunately persist despite rehabilitation efforts. The asymmetry of walking, alongside other factors such as obesity are heightened risk factors for the development of osteoarthritis. It is postulated that the risk of developing OA in the years following a stroke is increased. However, there is a dearth of information available in terms of the typical knee loading profiles, which have been demonstrated as biomechanical impairments in knee osteoarthritis. in stroke survivors to determine the biomechanical risks of chronic stroke survivors developing OA. However, very little is known about the nature of knee load/moment patterns in stroke survivors to be able to test this hypothesis and determine the biomechanical risks of chronic stroke survivors developing OA. This is despite the fact that spatiotemporal asymmetry in other conditions (unilateral amputation and unilateral OA) is linked to the risk of developing knee OA. In these populations, some of the gait deviations seen in stroke (e.g. temporal gait asymmetry and excessive muscle activity), in the context of biological susceptibility, could contribute to secondary musculoskeletal complications, due to the cumulative effects of excessive and repetitive loading in long-term stroke. Nevertheless, it is not known to what extent the promotion of symmetrical gait patterns in stroke survivors affects knee joint loads.

Objectives: This research aims to characterise knee joint moments in a cohort of stroke survivors, compared to healthy, speed-matched participants. The secondary aim is to explore the immediate effect of imposing a symmetric gait pattern (based on spatiotemporal symmetry) on knee joint moments in stroke survivors and an asymmetric gait pattern on a healthy group, walking at the same speed. The last aim was to characterise knee joint moments in a cohort of stroke survivors over time (assessed on two occasions: at baseline and a two-year follow-up).

Methods: Kinematic and kinetic data were obtained with Three-dimensional (3D) motion analysis from 17 community-dwelling stroke survivors and 18 healthy older adults, walking over a six-metre walkway with embedded force plates, at their own, self-selected pace

(healthy older adults also walked at a slow pace, matched with the mean Self-selected Walking Speed (SSWS) of the stroke survivors). In the second study, the participants were asked to walk to temporal (metronome) and spatial targets (stepping targets on the floor), which either imposed asymmetry (for participants who were symmetrical in their usual walking) or symmetry (for participants who were asymmetrical in their walking). The final study was a retrospective case series study based on an analysis of secondary data gathered from a recruited stroke survivors' group, who had already participated in two previous studies as initial measurements with measurements being repeated at a two-year follow-up.

Results:

Study 1: The stroke survivors' (n=17) knee joint load (peak Knee adduction moment (KAM) and KAM impulse) did not exceed that of the healthy control group (n=18). In contrast, Knee Flexion Moment (KFM) was higher on the non-paretic side (p=0.024) in the cohort of stroke survivors, compared to the healthy controls walking at comparable speeds. In addition, KFM on both the paretic and non-paretic sides in stroke survivors' subgroups with less severe temporal (n=7) (mean=0.64[0.39] Nm/Kg for paretic and mean=0.58[0.30] Nm/Kg for Non-paretic side) and spatial (n=11) (mean=0.53[0.37] Nm/Kg for paretic and mean=0.57[0.29] Nm/Kg for Non-paretic side) asymmetries were higher than in the healthy controls (n=18) (mean=0.28 Nm/Kg, 95% CI= 0.16-0.40 Nm/kg), walking at comparable speed.

Study 2: The imposition of temporal and spatial symmetries on the stroke survivors with spatiotemporal asymmetry (n=13) did not show notable changes on knee joint moments (KAM and KFM) on the paretic and non-paretic sides.

Study 3: As a case series study (n=9)**,** the stroke survivors' knee joint load changed over time as KAM (peak and impulse) increases and KFM decreases on both sides. However, longitudinal changes of increase walking speed, increase pelvic drop and reduced knee ROM are commonly seen with knee joint moments changes overtime.

Discussion: The additional compensatory gait patterns (e.g. pelvic obliquity) and slow walking speed following a stroke provide the side effect of lowering knee joint moments during walking compared to healthy individuals. In contrast, other compensatory mechanisms (e.g. knee range of motion [RoM]) may increase the knee joint load (KFM) and then the risk of patellofemoral pain/OA. Furthermore, no changes were observed in knee joint moment/load (KAM and KFM) across stroke survivors after imposing spatiotemporal symmetry. The possible reason is the demonstrated nature of spatiotemporal asymmetry, in its relative resistance to change (on the imposition of symmetry). However, because with increasing age and high BMI following a stroke, the changes of knee joint loads (as a mechanical stimulus) may lead to the development of knee joint OA.

Conclusion: Stroke survivors' knee joint load (moment) is changing over time. However, joint moments appear to be heavily influenced by compensatory gait patterns. Such compensation, as well as the additional neuromuscular impairments, may produce a side-effect of lower frontal plane moment (KAM) and increase the risk of knee OA, due to the increased sagittal plane moment (KFM). Left unchanged, heightened KFM increases the risk of knee joint pain and OA. Knee joint moments did not manifest in notable changes as part of imposing symmetry on the stroke survivors. Furthermore, it is surprising that the stroke survivors with less spatiotemporal asymmetry displayed higher KFM than the healthy controls. These changes with time indicate the importance of considering how joint moments (as mechanical stimuli) change throughout the post-stroke lifespan, especially in light of the biological changes that usually accompany aging and increased Body Mass Index (BMI). However, future longitudinal work is necessary to investigate knee joint load from the very earliest stages of stroke recovery, taking into consideration cumulative load (physical activity), walking speed, and radiographic measurements of joint tissue.

Chapter 1: Introduction

For every 100 stroke survivors, around 75% present with mild to severe impairments that affect their cognition, sensory, motor, emotional and perceptual functioning (Sheffler and Chae, 2015). One of the main concerns for individuals who have suffered a stroke is the ability to regain their mobility and ambulatory function (Beyaert et al., 2015). Despite the majority of stroke survivors being able to walk independently after an extensive rehabilitation process (Alexander et al., 2009), walking speed is often reduced, muscle activity tends to be altered in some way, and timing and distance (spatiotemporal, kinetic and kinematic) asymmetry are prevalent between the lower limbs (paretic – affected side; non-paretic – less affected side). Thus, a number of associated factors could affect the stroke survivors' functioning (Patterson et al., 2014).

Researchers are increasingly turning to detailed gait analysis as a means of understanding the causes of persistent impairment, falls, and disability. Rehabilitation after stroke typically focuses on walking endurance and speed; as reflected in the prevalence of these as primary outcomes of clinical trials (Langhorne et al., 2009). However, achieving independent walking and normal gait pattern are a high priority for stroke patients during goal-setting in rehabilitation (Winstein et al., 2016). Post-stroke asymmetry has been extensively studied and investigated from a biomechanical point of view; being used as one of the fundamental indicators of walking ability, which provides a more advanced walking measurement than is possible using conventional measures such as speed. This helps clinicians and researchers to identify and track gait-related deviations in individuals with stroke (Patterson et al., 2012).

Improvements in hyper-acute medical treatment mean that long-term survival rates following stroke have steadily improved (Boysen et al., 2009), but impairments may still persist over a lifetime (Lakshminarayan et al., 2014). With growing emphasis on increasing physical activity (Billinger et al., 2014), as well as the biological changes that potentially accompany the aging process and obesity (Marini et al., 2001; Sheffler et al., 2014), it is important to understand the long-term potential for joint degeneration, where walking continues with altered gait mechanics. Persistent post-stroke alterations in gait pattern may play a role in mechanical stimuli; triggering biological processes that underlie the development of OA (Andriacchi et al.,

2015). Consequently, stroke survivors face more years of cumulative exposure to changes of a biomechanical (spatiotemporal symmetry, kinematics and kinetics) and biological (increasing age and BMI) nature, which may in turn cause their knee joints to be less adaptable to excessive/repetitive loading, resulting in knee OA. However, despite possible interaction between the biomechanical effects of hemiplegia and biological changes, very few studies have investigated the development of OA as comorbid in a stroke population, although they share the same risk factors.

Recent surveys have indicated the prevalence of comorbid joint arthritis and stroke, with 53% of stroke survivors presenting with arthritis of the joints, compared to 43% of individuals without stroke (Patterson and Sibley, 2016). Whilst it is not known whether OA precedes or follows stroke, it has been hypothesised (Norvell et al., 2005; K. K. Patterson et al., 2008) that gait asymmetry, which is characteristic of stroke, is associated with increased risk of musculoskeletal injury. Studies have reported increased pain (Hettiarachchi et al., 2011) and reduced femoral cartilage thickness on the paretic side in stroke survivors, compared to healthy individuals (Tunc et al., 2012). This suggests that following stroke, tissues may not adapt well to stroke-related changes in joint load. However, the cause of pain and cartilaginous changes has not yet been identified, as at least two years must elapse before the long-term effects of gait impairment on joint tissues and structures can be observed (Yang et al., 2005).

Although the precise pathophysiology of knee OA development/initiation is not clearly understood, it is typically considered as mechanically driven (abnormal mechanical loading), in the context of systemic susceptibility (Andriacchi et al., 2015). External knee joint moments (in the form of external knee adduction moments (KAM) and external knee flexion moments (KFM)) are used as surrogate loading measures, with established associations between increased KAM and KFM, and heightened risk of developing OA (Chehab et al., 2014; Thorp et al., 2006). However, factors such as walking speed play an important role in altering knee joint moments. Therefore, KAM impulse (loading over the duration of a stance phase) is thought to be a more sensitive predictor of OA risk than peak moment (de David et al., 2015; Robbins and Maly, 2009).

Changes in KAM and KFM following stroke can result from slower walking speed (increased

KAM impulse, due to greater stance time) (Kim and Eng, 2004; Perry et al., 1995; Robbins and Maly, 2009), altered knee range of motion (RoM), muscle co-activation (increasing patellofemoral joint reaction forces) (Chen et al., 2005; Creaby et al., 2013; Farrokhi et al., 2015; Hutin et al., 2012; Kim and Eng, 2004; B. Raja et al., 2012), and asymmetric knee joint moment profiles between the paretic and non-paretic limbs (Allen et al., 2011; Kim and Eng, 2003, 2004; Patterson et al., 2014; Teixeira-Salmela et al., 2001). Additionally, compensatory gait patterns are common after stroke, such as hip hiking (altering the frontal knee moment arm, due to ipsilateral pelvic obliquity and contralateral pelvic drop) (Chen et al., 2005; Chiba et al., 2016; Dunphy et al., 2016; Linley et al., 2010; Stanhope et al., 2014a), increased trunk lean (Van Criekinge et al., 2017), and toe-out and toe-in (Shull et al., 2013). These have also been known to contribute to changes in knee joint moment during walking (Shull et al., 2013). What it signifies is that internal knee joint structures must adapt to these potential changes in joint load, in order to prevent joint degeneration.

Despite the plethora of possible stroke-related biomechanical contributors to the development of knee OA, very few studies have investigated whether gait impairments following stroke (biomechanical asymmetries) alter joint moments (KAM and KFM), in a way that may be acknowledged as indicative of the risk of joint degeneration, or how these moments change (if applicable) in the course of long-term recovery. A preliminary study consisting of nine participants demonstrated that the post-stroke measurement of limb loading is feasible (Marrocco et al., 2016). The above study revealed high variability of peak KAM and KFM in stroke survivors; with some having higher moments on the paretic side and others, on the non-paretic side, compared to healthy adults (Marrocco et al., 2016).

However, as a result of variability between stroke survivors, it remains unknown whether gait impairments following stroke alter joint moments in such a way as to increase the risk of developing comorbid knee joint OA. Thus, whilst a great deal is known about spatiotemporal asymmetries following stroke, relatively little is known about kinetic asymmetries, particularly those relating to KAM and KFM, which may indicate a biomechanical mechanism for the development of comorbid OA. Therefore, studies that characterise knee joint moments (reflecting loading) over longer-term stroke recovery are lacking. Clinically, a definitive understanding of the presence of loading patterns, which are known to be risk factors of the development of knee OA following stroke, is important, because this could help

clinicians prioritise gait rehabilitation goals and thus, limit the potential risk of joint degeneration, while at the same time promoting physical activity.

In light of the above, a better understanding of joint loading in the years following stroke and/or after improving gait symmetry could help prioritise rehabilitation goals, as a means of limiting potential knee joint degeneration in the long term. In addition, it could assist with early diagnosis, prevention, and the provision of proper interventions for such morbidity; thereby avoiding any further complications and enhancing the speed of recovery. Therefore, this thesis sets out to explore the impact of lower limb asymmetry on knee joint biomechanics, especially in reference to mechanical loading, by quantifying the knee joint load and exploring the potential risk of knee OA.

1.1 Thesis Aims

The aim of this thesis is to characterise stroke survivors' knee joint moments, cross-sectionally, longitudinally, in comparison to healthy participants, and after manipulating the spatial and temporal asymmetry of their gait.

1.2 Thesis Overview

Chapter 2 of this thesis provides a comprehensive review of the relevant literature in this area; describing the stroke survivors' gait patterns, including post-stroke gait asymmetry and the potential biomechanical risk factors for the development of musculoskeletal injuries. In addition, it explores the pathophysiological mechanism of initiation/progression on knee joint OA; while the risk factors, abnormal loading, and joint load measurements are defined and discussed in relation to survivors of stroke and other conditions. The chapter then ends by exploring joint moments in gait, where there are unilateral joint conditions (i.e. post-stroke), along with the potential progression and development of knee OA. In light of the above, the research questions and study hypothesis are subsequently presented.

Chapter 3 of this thesis provides the main methodological details of the study; designed to address the research aim and objectives. Moreover, in this chapter, the repeatability of the investigators' marker placements on the lower limbs and various planes was evaluated, according to the gait measures.

Chapter 4 addresses the question: 'Does knee joint loading in long-term stroke recovery indicate a risk of joint degeneration?' by exploring the difference in knee joint moment amongst stroke survivors; looking at it from different perspectives (between sides, based on the severity of the spatiotemporal asymmetry and compared to healthy controls walking at self-selected (SS) and slow walking speeds).

Chapter 5 reports on the immediate effect of imposing spatially and temporally symmetrical and asymmetrical gait patterns on knee joint moment profiles.

Chapter 6 contains a retrospective series of case studies, aimed at characterising stroke survivors' knee joint load/moments over time (assessed on two occasions: at baseline and at a two-year follow-up).

Chapter 7 presents the overall discussion and conclusion to this thesis.

Chapter 2: Literature review

The aim of this chapter is to investigate the current literature on stroke gait asymmetry, the pathophysiology of knee joint OA and its risk factors, and the potential risk of OA in individuals, post-stroke, as a consequence of gait asymmetry. This chapter begins with the epidemiology of stroke and defines the prevalence of post-stroke gait asymmetry in spatiotemporal, kinematic, and kinetic terms. As mechanical loading (knee joint moment) is thought to play an important role in the risk of OA of the knee, a search strategy was adopted here to identify the relevant publications on knee joint moments on different planes in stroke survivors. The section then explores the pathophysiological mechanism of initiation/progression of knee joint OA and the risk factors involved. Following this, the measurement of knee joint load and the factors influencing knee joint moment (KFM) and KAM are presented. The chapter then ends by exploring joint moments in gait, where there are unilateral joint conditions (i.e. post-stroke), along with the potential progression and development of knee OA; ending with the research questions and thesis hypothesis.

2.1 Stroke epidemiology

Stroke is a major health burden that leads to morbidity and mortality in the United Kingdom and worldwide. In 2018, it was estimated that around 110,000 strokes occur in England each year (Stroke Association, 2018). Worldwide, the World Health Organization (WHO) reports that approximately 15 million people suffer a stroke each year. Of these, five million die and another five million are considered as disabled, placing an increased burden on families and communities. For every 100 stroke survivors, around 75% present with mild to severe impairments, which can affect cognitive, sensory, motor, emotional, and perceptual functions (Sheffler and Chae, 2015). One of the main concerns for anyone who has suffered a stroke is regaining mobility and ambulatory function (Beyaert et al., 2015).

Despite the majority of stroke survivors being able to walk independently after an extensive rehabilitation process (Balaban and Tok, 2014), there may be a reduction in walking speed and alterations in muscle activity, with timing and distance (spatiotemporal, as well as kinetic and kinematic) asymmetry being prevalent in the lower limbs (paretic – affected side; non-paretic – less affected side). This can in turn lead to several associated factors that affect the

way in which stroke survivors function (Balaban and Tok, 2014; Beyaert et al., 2015).

Given that the majority of stroke survivors who regain a basic walking pattern continue to experience disability (the majority do not regain full independent mobility in the community) and falls (50% of community-dwelling stroke survivors suffer falls) (Peters et al., 2016), researchers are increasingly turning to detailed gait analysis, in order to understand the causes of persistent impairment, compensatory mechanisms, falls, and disability. Rehabilitation after stroke typically focuses on walking endurance and speed, as reflected by the prevalence of such factors as primary outcomes in clinical trials (Langhorne et al., 2009). However, achieving independent walking and normal gait pattern are of a high priority for stroke patients during goal setting in rehabilitation (Winstein et al., 2016).

Walking, as classified by the International Classification of Function, Disability and Health (ICF), is a health and health-related domain of the Activities and Participation component (World Health Organization, 2001). Therefore, working on the recovery of impaired movement, with regard to walking (function) receives most attention in post-stroke therapy (Langhorne et al., 2009). However, the potential for stroke survivors to regain a basic walking pattern is complex, and the process may follow different paths; for example, true recovery or compensation. In fact, it is claimed that motor recovery after stroke occurs, to a large extent, through behavioural compensation, rather than processes of true recovery alone (Hylin et al., 2017; Levin et al., 2009). Therefore, during walking, stroke survivors develop various compensatory or asymmetry strategies, in response to the insufficient return of nerve system function and in order to achieve a functional and safe gait pattern (Levin et al., 2009; B. Raja et al., 2012). Therefore, understanding post-stroke gait patterns and mechanisms to aid mobility and the consequences of each will help to improve the efficacy and success of rehabilitation strategies after injury (Langhorne et al., 2009; Levin et al., 2009).

2.2 Post-stroke gait asymmetry

Post-stroke gait asymmetry has been extensively studied and investigated from a biomechanical point of view and has been utilised as one of the fundamental indicators that enables an insight into walking ability. More detailed measures of walking (as opposed to

crude measures of speed) could aid clinicians and researchers to identify and track gait-related deviations in individuals with stroke (Patterson et al., 2012). Post-stroke gait asymmetry has been described in the literature with respect to different parameters: spatiotemporal (distance and timing), motion (kinematics), and force (kinetics) (Beyaert et al., 2015; Wonsetler and Bowden, 2017a). The asymmetry of gait after stroke has been proposed to be due to several factors, including walking speed, muscle weakness and spasticity, and inappropriate muscle contraction (Chu et al., 2015; K. K. Patterson et al., 2008; B. Raja et al., 2012). However, the variability and severity of asymmetry has been attributed to the heterogeneity of individuals after stroke (Tyrell et al., 2015).

2.2.1 Spatiotemporal asymmetry

Compared to the relative paucity of information on kinetic parameters, spatiotemporal parameters are the most commonly reported measures for analysing symmetry in individuals after stroke (total sample size of n=507; see (Wonsetler and Bowden, 2017a)). In addition to their importance for determining balance and functional independence (K. K. Patterson et al., 2008), spatiotemporal parameters are commonly reported, because they require less advanced technology to quantify them, compared to kinetic and kinematic variables.

According to Patterson et al. (2008; 2014), spatiotemporal asymmetry may be found amongst independent walkers, poststroke. In this sense, the above authors found that between 55.5% and 59% of chronic stroke patients showed significant temporal asymmetry (using stance time, single stance time, double support time and swing time parameters), while 33.3-49% showed significant spatial asymmetry[1] (mainly using a step length parameter). In temporal asymmetry, swing time and stance time are the most commonly described parameters, with trends towards prolonged paretic swing time and/or prolonged non-paretic stance time, compared to the contralateral limb (K. K. Patterson et al., 2008; Titianova et al., 2003). Studies have reported that swing time asymmetry is mainly affected by impairment to the paretic side, such as dorsiflexion muscle weakness that impacts on foot clearness (Lin et al., 2006). In contrast, spatial asymmetry (step length) has been found to vary across studies in terms of

[1] The classification of asymmetries was based on a normative cut-off ratio of 1.06 for swing symmetry and 1.08 for step length symmetry.

the magnitude and direction of asymmetry between limbs (K. K. Patterson et al., 2008; Roerdink and Beek, 2011).

Previous literature has suggested that post-stroke, individuals display longer paretic step length, because of lower paretic side foot propulsion. This weak propulsion force of the paretic side affects the forward progression of the contralateral side (non-paretic side), resulting in short step length in the non-paretic side (Balasubramanian et al., 2007; Hsu et al., 2003). However, Kim and Eng (2003) report that increased step length in chronic stroke survivors (n=28) is not only present in the paretic limb, but can also be found in the non-paretic limb (with the number of post-stroke participants exhibiting longer paretic/non-paretic steps amounting to 14/14). Inconsistencies in the direction of the step length asymmetry across stroke survivors is supported by Roerdink and Beek (2011), who sought to understand the variation in the direction of step length asymmetry among chronic post-stroke subjects (n=10). The results showed that forward foot placement, and trunk progression asymmetries and their contribution were responsible for the step length asymmetry and directional variation. However, the variation between studies in identifying the direction of step length asymmetry in any subgroup of stroke survivors may be due to heterogeneity in the clinical presentation of stroke, as well as to the complex relationships between the many prognostic factors that can contribute to step length asymmetry (Roerdink and Beek, 2011) – such as the site and side of the injury, and the severity of the stroke.

2.2.2 Kinematic asymmetry

The measurement of joint angle kinematic and kinetic parameters during walking can help to understand and identify the causes and mechanisms of asymmetry. Compared to healthy individuals, joint kinematics (i.e. joint angle trajectories) in individuals who have suffered a stroke will exhibit differences in peak joint displacement of the lower limb, or excursions on all planes while walking on the paretic and non-paretic sides (Kim & Eng, 2004). However, there is wide variation in the magnitude of range of motion (ROM) between joints in the lower limbs. Although no systematic review has hitherto been undertaken on post-stroke joint kinematics, some recent narrative reviews(Beyaert et al., 2015; Sheffler and Chae, 2015) indicate that common kinematic deviations in the lower limbs comprise the following:

- *Sagittal plane*: the paretic side shows a decrease in hip, knee and ankle joint

excursions (Olney & Richards, 1996), with increased plantarflexion at initial contact (Olney & Richards, 1996) and toe-off (Chen et al., 2005) in the ankle joint, occasional knee hyperextension in the stance phase, and decreased knee flexion and minimal dorsiflexion during swing (Kim & Eng, 2004; Lamontagne et al., 2007). However, the non-paretic side will show an increase in hip, knee and ankle joint magnitude when compared to the affected side (Kim & Eng, 2003; Chen et al., 2005), except for the ankle joint, where plantar flexion at toe-off will reveal some decrease (Chen et al., 2005).

- *Frontal plane*: there is an increase in lateral pelvic tilt, hip abduction, knee adduction, and ankle joint movements on the paretic side (Kim & Eng, 2004; Chen et al., 2005; Lamontagne et al., 2007; Chen et al., 2010) and an increase in hip and knee joint magnitude on the non-paretic side (Chen et al., 2005).
- *Transverse plane*: the paretic hip and ankle joints have been found to show abnormally large external rotations throughout the gait cycle (Lamontagne et al., 2007), but Chen et al. (2005) showed that the range of the knee and ankle joints on the non-paretic side is slightly higher than on the paretic side. Moreover, hip joint RoM on both sides is almost identical in post-stroke individuals.

2.2.3 Kinetic asymmetry

A limited number of previous studies on stroke survivors have referred to the changes in the magnitude of kinetic profile (involving forces, work, energy, power and moments) in both limbs and in the symmetry of these variables between limbs while walking, compared to healthy participants (Wonsetler and Bowden, 2017b). Moreover, changes in the magnitude of kinetic variables in individuals with stroke is reported as relating to other factors, such as walking speed, residual impairments, and functional recovery and capacity (Beyaert et al., 2015; Wonsetler and Bowden, 2017b). While the significance of kinetic asymmetry (especially knee joint moment) between sides in stroke survivors remains unclear, a search strategy was conducted here to identify relevant publications/studies in this regard (see Appendix A.7). The results revealed just ***four studies*** (with a total sample size of n=98) that report kinetic asymmetry (knee joint moment) between sides on different planes (Allen et al., 2011; Kim and Eng, 2004; Marrocco et al., 2016; Teixeira-Salmela et al., 2001). However, while there are four papers that explore knee joint moment in stroke survivors, only one study has compared

the paretic and non-paretic sides (statistically), and this was on the sagittal plane (Allen et al., 2011).

In one of very few relevant studies, Teixeira-Salmela et al. (2001) showed asymmetry in the kinetic profile between limbs among chronic stroke (n=13) patients on the sagittal plane only. The baseline results revealed an increase in most of the external overall peak joint moments (i.e. hip flexion, knee flexion, and ankle dorsiflexion and plantar flexion) on the non-paretic side, compared to the paretic side, except for an increase in the knee extension moment on the paretic side (see Table 2-1)**.** However, in addition to having a small sample size of just 13 participants, 10 of the stroke survivors sampled used assistive devices while walking, which was reported to affect the kinetic magnitudes (Polese et al., 2012). Moreover, although knee joint moments were quantified for all lower limb joints, the overall peak joint moment waveform was the only part reported.

Table 2-1: Peak moments

Study	N	plane		Join kinetic								
				Hip			Knee			Ankle		
				P	NP	SR.	P	NP	SR.	P	NP	SR.
(Teixeira-Salmela et al. 2001)*	13	Sag.	Flex/Plflex	0.34(0.22)	0.5(0.43)	1.5	0.25(0.21)	0.20(0.11)	1.25	0.91(0.26)	1.17(0.41)	1.28
			Ext/Doris	0.59(0.23)	0.6(0.17)	1.02	0.32(0.31)	0.50(0.33)	1.56	0.08(0.10)	0.11(0.12)	1.37
(Kim and Eng, 2004)*	20	Sag.	Flex/Plflex	0.32(0.21)	0.41(0.23)	1.28	0.30(0.20)	0.20(0.12)	1.5	0.64(0.22)	1.10(0.25)	1.71
			Ext/Doris	0.33(0.17)	0.60(0.25)	1.81	-	-	-	-	-	-
		Front.	Abd/inv.	0.68(0.23)	0.93(0.23)	1.36	0.24(0.17)	0.30(0.15)	1.25	0.17(0.13)	0.17(0.11)	1.0
			Add	-	-	-	-	-	-	-	-	-
		Trans.	Int.R	0.06(0.04)	0.10(0.05)	1.66	0.05(0.01)	0.06(0.05)	1.2	-	-	-
			Ext.R	0.07(0.03)	0.15(0.06)	2.14	-	-	-	-	-	-
(Marrocco et al. 2016)γ	9	Sag.	Flex	-	-	-	1.26 (1.13)	1.10(1.20)	1.15	-	-	-
		Front.	Add	-	-	-	2.64(0.98)	2.23(0.62)	1.18	-	-	-

Legends: (Ext) extension, (Flex) flexion, (Plflex) plantarflexion, (Dorsi) dorsiflexion, (Abd) abduction, (Add) adduction, (Inv) inversion, (IR) internal rotation, (ER) external rotation, (Sag) sagittal, (Front) frontal, (Trans) transvers, (P) paretic, (NP) non-paretic, (SR) symmetry ratio=large value/small value. (*) Peak moments in this table represent the overall internal peak moments. (γ) External moment: 1st peak for adduction and overall peak for flexion moments.

Another study, by Kim and Eng (2004), found that a sample of chronic stroke patients (n=20) showed a variation in their kinetic profile data on all planes and in all joints between limbs. The above results showed that most of the overall peak external hip joint moments investigated (i.e. flexion, extension, internal rotation, and external rotation) were increased

on the non-paretic side, compared to the paretic side. Meanwhile, the knee joint moment on the non-paretic side demonstrated an increase in KAM and internal rotation moments, but a decrease in the knee flexion moment. At the ankle joint, the plantar flexion moment was reduced on the paretic side, while the inversion moment was similar for both sides. Nevertheless, despite these asymmetrical results for the kinetic variables between limbs, the differences between the paretic and non-paretic sides were not statistically compared (see Table 2-1). Therefore, the lack of comparison with a control group, the use of the overall peak of the moment and the use of assistive devices with some of the recruited stroke survivors were the main limitations of this study's results.

Allen et al. (2011) investigated the relationship between chronic stroke survivors (n=55), grouped by step length asymmetry (high (n=29), symmetrical (n=17), and low (n=9) groups) and lower limb joint moments. The above study showed that, compared to the healthy participants, the paretic leg ankle moment impulse was decreased in all the post-stroke subjects. In addition, the individuals with a longer paretic step length (the high group) demonstrated increased non-paretic ankle dorsiflexion and knee extensor moment impulses, while the participants with a shorter paretic step (the low group) displayed no significant changes. Aside from this, the symmetrical group, compared to the control group, had increased bilateral hip flexor moment impulses. Notwithstanding this, despite the ankle joint showing significant differences between the paretic and non-paretic sides in the stroke groups; the knee and hip joints revealed no significant differences between sides in terms of moment impulses. However, this study utilised a split-belt treadmill, which was found to change the magnitude of the kinetic variables on the sagittal plane (i.e. increased hip extensor, decreased knee extensor, and decreased dorsiflexion moments), in comparison with over-ground walking (Lee & Hidler, 2008). Thus, the true differences between a stroke survivor population and a healthy aged-matched cohort is still lacking in the literature in terms of three-plane joint kinetics.

One recent study by (Marrocco et al., 2016) aimed to determine the feasibility of measuring joint kinetics (dynamic knee joint loading) and characterising knee loading patterns (external knee flexion and adduction moments) in post-stroke individuals (n=9) during walking. The main finding of the above study showed that measuring knee joint loading (as represented by

KFM and KAM) was feasible. Despite these asymmetrical results between sides (higher on the paretic side's KFM and KAM) (see Table 2-1), the difference between sides in stroke survivors was not compared statistically. Moreover, in addition to the lack of statistical analysis, a small sample size, and the type of participants recruited (young, high-functioning stroke survivors, aged 57.7± SD 9.8 years) were the main limitations of this study.

While we know a great deal about the spatiotemporal asymmetries of post-stroke gait, we have relatively little in-depth information about the nature of its kinetic profile (for all three planes of movement). Moreover, to date, we do not know the consequences of persistent asymmetry (Patterson et al., 2014). There are indications from some studies that asymmetry in walking is detrimental and related to poor metabolic and mechanical efficiency (Lamontagne et al., 2007), restricted functional mobility outcomes, and increased risk of falling (Balasubramanian et al., 2009) and musculoskeletal comorbidities (Hettiarachchi et al., 2011; Karatepe et al., 2008; Kuptniratsaikul et al., 2009). However, few studies have examined kinetic asymmetry in stroke survivors. The studies that do exist show a complex relationship between asymmetry and related prognostic factors (age, severity of stroke, side of paresis, etc.) (Patterson et al., 2010). Indeed, the finding that other conditions differentially affecting just one limb (such as amputation and knee OA) increase the risk of developing knee OA (Jones et al., 2013; Morgenroth et al., 2014; Shakoor et al., 2002; Struyf et al., 2009) lends support to the notion that stroke-related gait impairments, which affect limbs asymmetrically and persist after rehabilitation efforts, may also lead to the development of joint stresses and the development of OA in the knees of stroke survivors. If this is also true within the stroke population, then future treatments should seek to reduce this consequence, although this is not yet known. Importantly, the long-term care of individuals through post-stroke rehabilitation would also be an avenue for intervention, especially if the stroke survivors are at risk.

2.3 Osteoarthritis

OA is a common degenerative joint disease, prevalent in middle-aged and older adults and resulting in heavy social and economic burdens (Palazzo et al., 2016). It can occur in any synovial joint, such as the knee, hip, hands or feet (Palazzo et al., 2016). Joints with OA are characterised by articular cartilage damage and subchondral bone remodelling, leading to

impairments such as joint pain and stiffness, muscle dysfunction, and functional limitations (Bastick et al., 2015). Globally, the prevalence of OA is increasing and it has been considered as the most common musculoskeletal and joint disease, due to increasing average age of the population in developing countries and a rise in age-related and lifestyle risk factors of OA (Palazzo et al., 2016). In the US, it has been estimated that 26 million people over the age of 25 have some form of clinical OA (Lawrence et al., 2008), while in the UK in 2010, the number of people seeking treatment for OA was 4.7 million, which is expected to rise to 8.3 million by 2035 (Arthritis Research UK, 2013). OA may occur in any joint but is most common in the joints of the lower extremities: the hips and knees. The existence of OA in lower limb joints is one of the leading causes of functional limitation and disability in the lower extremities (Bastick et al., 2015).

2.3.1 Knee Osteoarthritis (OA)

The incidence and prevalence of knee joint OA is considered to be the highest amongst all other weight-bearing joints (Palazzo et al., 2016). The presence of knee OA is defined according to two main categories: radiographic OA and symptomatic OA (Pereira et al., 2011). Knee OA is generally defined using radiographic classification criteria for classifying and grading OA. In this sense, the Kellgren and Lawrence (KL) score is widely used as an objective measure to grade the severity of the disease (Hunter, 2011). Rather than being based on symptoms, the above score is based on observations of characteristic features of the disease in the joint x-ray, such as narrowing joint space, osteophytes, subchondral sclerosis and cyst formation. Kellgren and Lawrence grades range from 0-4, as follows: (0) Normal; (1) Doubtful narrowing of joint space, possible osteophyte development; (2) Definite osteophytes, absent or questionable narrowing of joint space; (3) Moderate osteophytes, definite narrowing some sclerosis, possible joint deformity, and (4) Large osteophytes, marked narrowing, severe sclerosis and joint deformity (Hunter, 2011).

Symptomatic knee OA is generally defined as the existence of joint radiographic changes in combination with certain symptoms, including pain, aching, or stiffness in the affected joint (Pereira et al., 2011). Therefore, x-rays should not be used in isolation to assess OA, because they will not differentiate between symptomatic and asymptomatic OA.

2.3.1.1 Pathophysiology and Risk Factors of Knee Joint Osteoarthritis (OA)

As reported earlier, knee joint OA is a heterogeneous disease that is characterised by progressive cartilage degeneration and subchondral bone changes. However, knee joint OA is a disease that affects all joint compartments, including the subchondral bone, ligaments/tendons, capsule, synovial membrane, formation of osteophytes, and periarticular muscles, as well as bringing about the loss of articular cartilage (Mobasheri and Batt, 2016). Although the aetiology and pathophysiology mechanism is unclear, knee OA appears to be a complex disorder, which includes genetic, biochemical and mechanical factors, since joint cartilage is the key component of the disease process (Andriacchi et al., 2015). However, in order to improve our understanding of the pathophysiology of knee joint OA, the natural mechanical and biological properties of articular cartilage first need to be considered.

Articular Cartilage

Articular cartilage is the thin, flexible and mechanically compliant connective tissue, which is located at the end of the bones in all synovial joints (Halloran et al., 2012). It provides a frictionless surface for articulation, thus playing an important role in ensuring the even distribution of load across the joints and preventing degeneration in the articulating surfaces (Sophia et al., 2009).

Healthy articular cartilage consists of avascular tissue, in which an extensive **extracellular matrix** (ECM) comprises two primary phases: liquid and solid. The liquid phase involves high water content (70-78%) and inorganic salts such as sodium, potassium and calcium (Sophia et al., 2009). In contrast, the solid phase consists of a highly organised and dense network of collagen fibres, **proteoglycans** (complex molecules composed of a core protein) and **chondrocytes** (Xia et al., 2014). Importantly, chondrocyte cells (the only cell type in the articular cartilage) plays a vital role in maintaining tissue homeostasis (steady internal conditions). They also respond to structural changes/injury in the surrounding cartilage matrix, during physiological loading (Akkiraju and Nohe, 2015). However, articular cartilage has a very limited ability to self-repair any damage to its components, because of the lack of vascular innervation (Sophia et al., 2009).

Anatomically, articular cartilage is divided into four layers (zones): superficial, middle/transitional, deep, and calcified (see Figure 2-1). The superficial zone represents the top layer of cartilage, forming 10-20% of its total thickness; it consists of a number of chondrocyte cells and layers of collagen fibres, which are arranged in parallel (horizontally) with the plane of the articular surface. Due to the arrangement of the collagen fibres in this zone, it is thought to provide the most resistance to shear and tensile forces (Sanchez-Adams et al., 2014; Sophia et al., 2009)

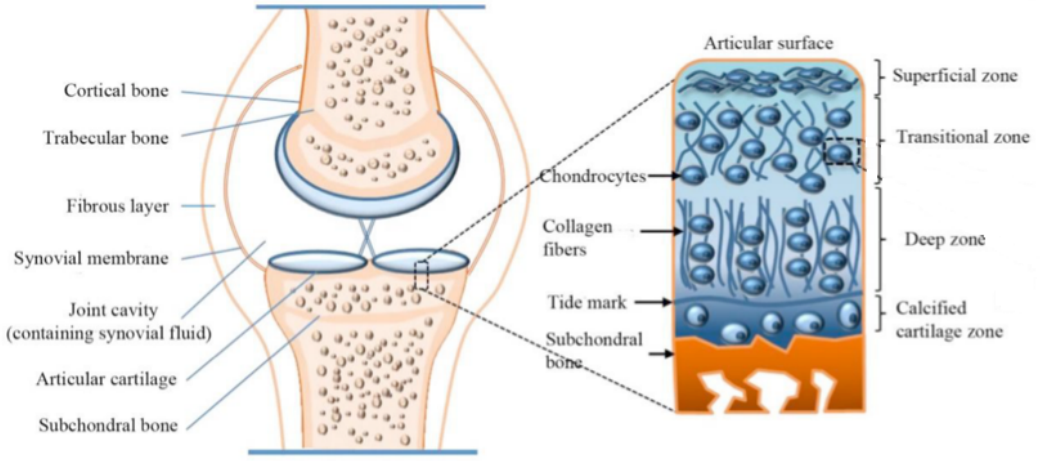


Figure 2-1: The morphology of articular cartilage zones (superficial, middle/transitional zone, deep, and calcified cartilage zones) and subchondral bone in normal cases (adapted from (Martel-Pelletier et al., 2016)

The middle/transitional zone represents 40-60% of the total thickness of the cartilage. It is referred to as 'transitional', because of the random transitional arrangement of (oblique) collagen fibre layers, lying in both horizontal directions (in the superficial zone) and vertically (in the deep zone). In comparison with the superficial zone, this middle zone has thicker collagen fibres, known as proteoglycans, as well as rounded, low-density chondrocyte cells. These characteristics of the zone attract high water content, which, together with the thick collagen fibres, acts as a mechanical cushion to withstand and absorb the compressive forces transmitted to the joint.

The deep zone forms 20-50% of the total thickness of the cartilage. It has the lowest water and collagen fibre content, but the highest proteoglycan content, compared to the previous zones. However, the collagen fibres in this zone are the widest in diameter and are vertically oriented (in addition to the chondrocyte cells), along the vertical axes of the articular surface.

The arrangement of the collagen fibres in this zone provides the highest degree of resistance to compressive forces. The final layer of the articular cartilage is the calcified zone, which is separated from the other zones by a tidemark, which distinguishes between the non-calcified and calcified areas. The calcified zone contains minimal water, chondrocytes and collagen fibres, compared to the other zones and it works to anchor the cartilage to the subchondral bone (Martel-Pelletier et al., 2016; Sanchez-Adams et al., 2014; Sophia et al., 2009).

Cartilage Changes/Deformation

As reported earlier, the mechanical and biological properties/components of articular cartilage play an important role in facilitating the transmission of load with a low frictional coefficient. Under physiological loading, the components of articular cartilage tissue are altered in their volume and internal pressure (Sophia et al., 2009). This deformation in the articular cartilage leads to an interaction between the materials associated with the liquid and solid phases (due to the biphasic nature of articular cartilage) (Sanchez-Adams et al., 2014).

As a result of joint loading, the increase in internal pressure causes fluids to flow out through the pores of the sold ECM. This process causes frictional resistance within the tissue, reinforcing the viscoelastic/deformation behaviour of the articular cartilage, so that it can withstand the force exerted upon the joint. Later, once the load on the joint is removed, the fluid in the ECM tissue will flow back into the tissue via highly negatively charged proteoglycans (Lotz and Loeser, 2012). ***However, the joint cartilage responses to mechanical loading are highly dependent on load features, such as loading amplitude frequency, strain-rate and loading history*** (Sanchez-Adams et al., 2014). Moreover, the ability of articular cartilage to withstand long-term mechanical loading will depend on its biomechanical and biological properties (Sophia et al., 2009). The failure of these properties to suitably respond to ECM tissue changes/alterations after loading may result in tissue pathology and degeneration, of which knee joint OA is a prime example.

2.3.1.2 Risk Factors

The aetiology of OA is multifactorial, containing systemic factors that include age, gender,

race/ethnicity and genetics, as well as local biomechanical risk factors, such as obesity, joint malalignment and deformity, history of joint trauma, abnormal and/or asymmetric gait mechanics, and certain sporting activities and occupations (see Figure 2-2)(Felson et al., 2000; Zhang & Jordan, 2010). Although the precise pathophysiology of knee OA development/initiation is not clearly understood, it is typically considered as mechanically driven within the context of systemic susceptibility (Andriacchi et al., 2015).

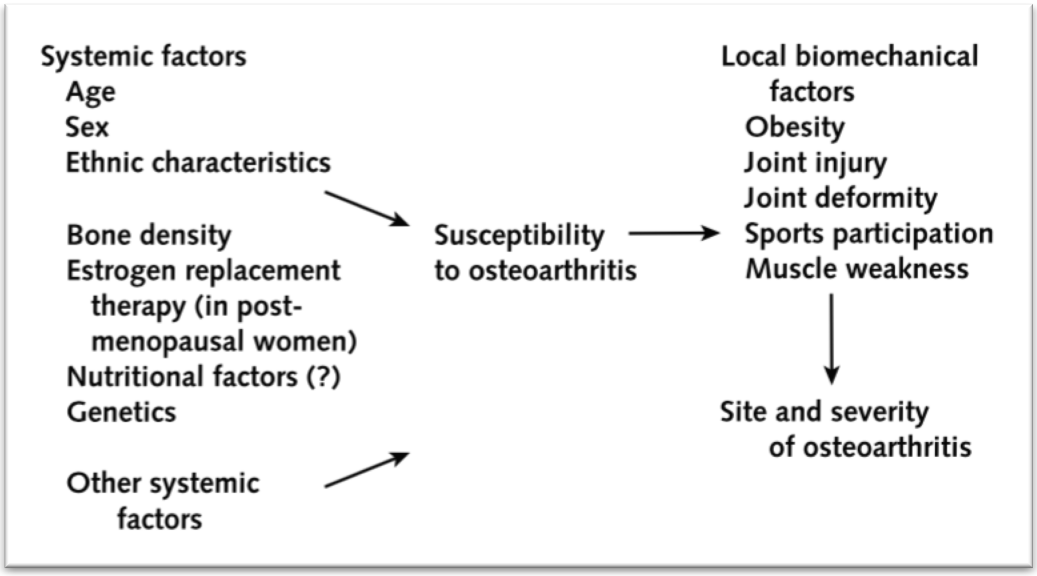


Figure 2-2: OA risk factors (Felson et al., 2000)

According to the previous reviews that determine the prognostic factors for knee OA (Blagojevic et al., 2010; Felson, 2004), there follows a short synopsis of the main risk factors of knee OA.

Systemic Factors:

Age

Age is the one of the main and most serious risk factors predicting the development and progression of knee OA. For example, it has been found that the incidence of knee OA increases remarkably after the age of 50 (Felson and Zhang, 1998; Johnson and Hunter, 2014). According to Jordan et al. (2007) based on a cohort study, the prevalence of symptomatic knee joint OA rose from 16.3% to 32.8%, and prevalence of radiographic knee OA rose from 26.2% to 50% in a 55-64 age group, compared to a +75 age group, respectively. Nevertheless, the mechanisms behind the association of knee OA with age are still not clear (Benderdour et

al., 2015; Loeser et al., 2016). However, it has been reported that OA may occur as a consequence of potential biological changes that accompany the aging process. These include the reduced ability of articular cartilage tissues to stimulate repairs; unstable joints, due to hypermobility; decreased muscle strength, and slow peripheral neurological responses (Greene and Loeser, 2015; Palazzo et al., 2016).

Studies on extraocular matrix components have suggested that age determines the composition of articular cartilage; with increasing age, the synthetic function of the chondrocytes in all articular cartilage zones show decline/alteration, because of changes in the distribution of these cells (which dissipate in the superficial zone and increase in the deeper zones) (Lotz and Loeser, 2012). In contrast, pathogenic studies have claimed that the aging process contributes to the death of chondrocyte cells (Lotz and Loeser, 2012). As a result, chondrocyte dysfunction/disturbance has been found to play an important role in increasing the prevalence of OA and impairing the ability of articular cartilage to repair itself (Akkiraju and Nohe, 2015; Loeser et al., 2016).

As reported earlier, the ECM is composed of water, a network of collagen fibres, and large amounts of proteoglycans (Sophia et al., 2009). However, age-related changes in cartilage are found to affect ECM hydration, cell density and volume, due to reduced proteoglycan and collagen fibre functioning (Loeser et al., 2016). The interaction between proteoglycans – as the main determinant of water content in articular cartilage – and collagen fibres, renders the ECM highly hydrophilic and enables it to resist compressive mechanical loading. However, with increasing age, ECM hydration is reduced, and the collagen fibres become less thick. consequently, articular cartilage shows a gradual decrease in its thickness and an increase in its compressive stiffness and risk of OA. The examples of magnetic resonance imaging (MRI), reproduced in Figure 2-3, below, illustrate the change in ECM thickness with increasing age (Lotz and Loeser, 2012).

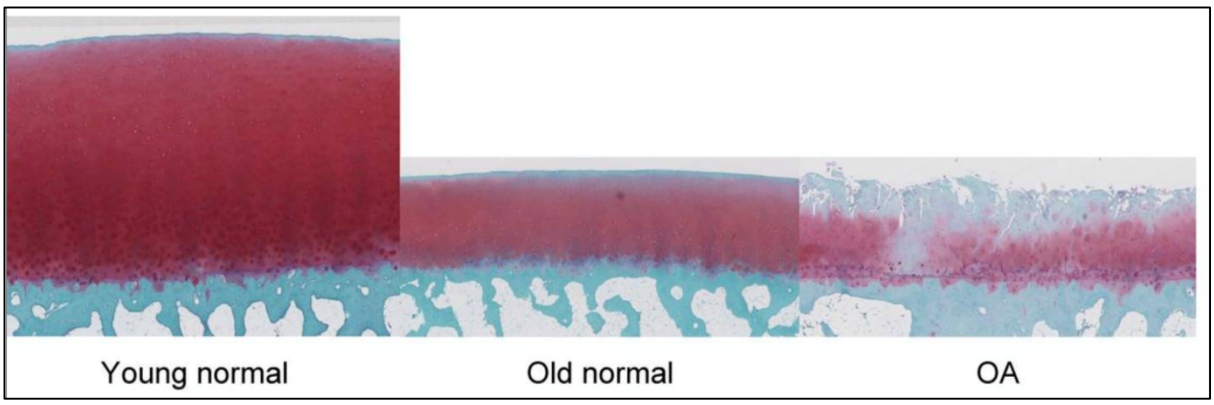


Figure 2-3: Image showing 'Young normal' (left, age 40), 'Old normal' (centre, age 76), and 'OA donor' (right, age 88). The samples illustrate the reduction in ECM thickness with age (adapted from (Lotz and Loeser, 2012)

Gender (Sex)

OA affects both males and females, but it generally occurs more amongst women (Srikanth et al., 2005). However, it has been reported that the incidence of OA is higher in men before the age of 55, but women show a higher prevalence and incidence after the age of 50 (Felson and Zhang, 1998). According to Srikanth et al. (2005), elderly women are at high risk of OA, because of postmenopausal oestrogen deficiency, which plays an important role in increasing the risk of OA, particularly in the knee joint. Based on experimental and observational studies, oestrogen has been shown to be of some relevance to the homeostasis of joint tissue and its healthy status, via several complex molecular mechanisms (Roman-Blas et al., 2009).

Ethnic Characteristics

Ethnicity is one of the factors that determine whether there is any risk of developing knee joint OA. For example, according to one study by Zhang et al. (2001), the prevalence of knee joint OA (radiographic and symptomatic) is significantly higher in Chinese women from Beijing than it is amongst white women from United States.

Bone Density

Numerous studies have consistently reported the positive association between high bone mass density (BMD) and the risk of radiographic knee OA (Blagojevic et al., 2010). Although the mechanism underlying this risk is still unclear, as mentioned earlier, these studies have indicated narrowing joint space and osteophyte formation as the possible mechanism,

following increasing BMD (thickening of the subchondral bone) (Hardcastle et al., 2015). However, despite the reported positive association between BMD and knee OA, some area of controversy remains. A longitudinal study conducted over eight years showed that bone loss and the turnover of subchondral bone were associated with increased risk of knee OA progression (Zhang et al., 2000). Therefore, in light of this conflict, more studies are needed to draw a conclusion on the relationship between OA and BMD and the influence of genetic factors, which appear to be associated with BMD variation (Hardcastle et al., 2015).

Genetics

Amongst most of the biological risk factors of OA, the influence of genes appears to be one of the most influential in determining OA in all its forms. According to Palazzo et al. (2016), the aetiology of OA may be attributed to genetic factors, as it is responsible for 60% of all hand and hip OA, and 40% of knee OA.

Local Biomechanical Risk Factors

Obesity

A recent meta-analysis identified obesity as one of the main risk factors of OA in weight-bearing joints. The results showed a significant positive association between increased BMI and knee OA. In addition, the study indicated that every five units of increased BMI heightened the risk of knee OA by 35% (Jiang et al., 2012). Furthermore, systematic reviews of MRI studies have shown the effect of obesity on early structural changes in knee joint cartilage (Mezhov et al., 2014) and subchondral bone (Lim et al., 2014). Conversely, other studies have demonstrated the influence of weight loss on reduced risk of developing knee OA and increased early changes in knee structure (Christensen et al., 2007; Issa and Griffin, 2012; Mezhov et al., 2014; Wluka et al., 2013). The findings from these studies support the strong relationship between obesity, physical inactivity and risk (see Figure 2-4) of knee OA. However, the mechanism underlying the link between obesity and knee OA is complex and not completely understood.

Increased load on weight-bearing joints is perhaps considered to be the main contributing mechanism linking obesity to knee and hip joints(Issa and Griffin, 2012). However, obesity has also been found to increase the risk of OA on non-weight bearing joints such as hands (Visser

et al., 2014). This is evidence that joint load is not totally responsible for the risk of OA. Interestingly, obesity is considered to be a form of low-grade systematic inflammatory disease, which is closely associated with OA (Berenbaum et al., 2017).

Apart from the influence of mechanical loading, there is increasing interest in studying the effect of adipose (body fat) tissue, especially its contribution to the risk of OA by producing adipokines/leptin (pro-inflammatory substances), which have a negative effect on joint tissues (Dumond et al., 2003; Yan et al., 2018). The level of leptin in the blood of individuals with OA and rheumatoid arthritis was found to be higher than it is in healthy subjects (Otero et al., 2006). This high concentration of leptin may account for decreased joint ECM synthesis, leading to cartilage degeneration, especially where there is excessive joint-loading and/or a history of joint injury (Sanchez-Adams et al., 2014; Yan et al., 2018). According to Ku et al. (2009), the level of leptin in a joint's synovial fluid is positively correlated with the severity of the OA.

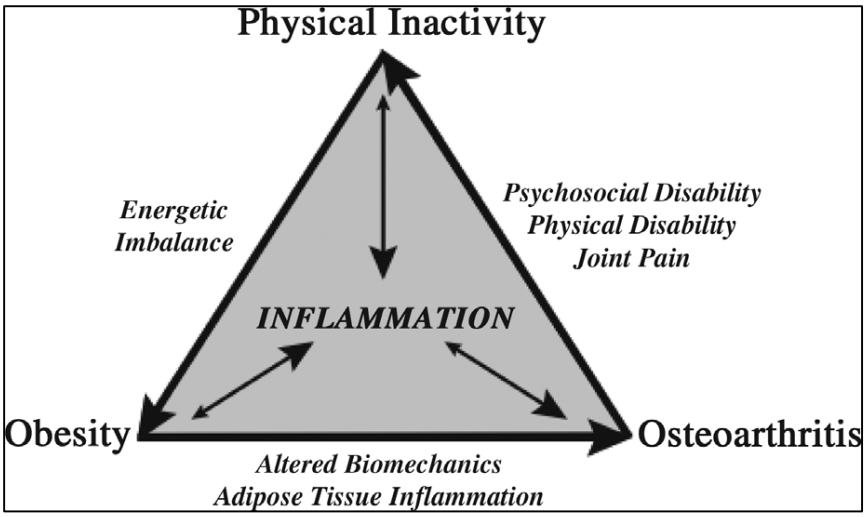


Figure 2-4: Progressive relationship among obesity, osteoarthritis, and physical inactivity(Issa and Griffin, 2012).

Joint Malalignment

Knee joint alignment in the frontal plane has been intensively investigated as one of the risk factors of OA (Tanamas et al., 2009). Biomechanically, knee joint varus (adduction) and valgus (abduction) moments play an important role in distributing load across knee joint compartments during walking (Tetsworth and Paley, 1994). If the joint deviates from neutral

its alignment, the stress of the physical load will be transferred to knee joint compartments that were not structured for such stress (Andriacchi et al., 2004). A systematic review conducted by Tanamas et al. (2009) showed that there is a strong relationship between joint malalignment and the progression of degenerative changes in knee joints.

Previous Joint Injury

Previous injury is one of the most important local biomechanical risk factors affecting all ages, and leading to subsequent knee OA (Zhang and Jordan, 2010). The distribution of internal compartments of the knee joint, due to certain types of injury – including meniscal, ligament, joint capsule or fracture injuries – does not directly damage the articular surface, but can lead to joint instability and will alter the normal load distribution; eventually leading to joint degeneration (Andriacchi et al., 2009; Buckwalter et al., 2013).

Muscle Strength/Weakness

In a recent meta-analysis, knee joint muscles and in particular, the knee extensor muscle, were indicated as playing an important role in stabilising the knee joint and absorbing shock. Therefore, the loss of extensor muscle strength will result in altering the mechanical stress on the knee joint and triggering symptoms of OA (Oiestad et al., 2015). In contrast to the above finding, however, increased muscle strength may also become a risk factor of knee joint OA. According to a recent longitudinal study (n=40121), conducted on a sample of young adult men aged 18 and then aged 24 at follow-up, greater knee extensor muscle strength is associated with increased risk of OA by middle age (Turkiewicz et al., 2017). Therefore, despite the conflicting findings in the literature, abnormalities in muscle strength (increasing or decreasing) may contribute to the risk of knee OA.

Abnormal Mechanical Load

In addition to the biological factors, abnormal mechanical loading of the knee joint has been found to be one of the key contributing factors to the onset and progression of knee OA (Andriacchi et al., 2015). Repetitive and excessive knee joint loading plays an important role in altering the distribution of normal loads between limbs and changing the balanced stress associated with functional activities, across the knee compartments (Andriacchi et al., 2015; Creaby et al., 2013; Farrokhi et al., 2015).

During walking, as a primary daily activity, knee joints experience cyclic mechanical loading. This load has been found to place stress on the internal structures of knee joint, which are constructed to distribute such stress between compartments within the knee (Andriacchi et al., 2015; Farrokhi et al., 2015). Accordingly, there are two main ways in which the knee distributes the loads experienced during walking: through the role of external moments around the knee, and through the contribution of the muscles, ligaments and cartilage to support these moments (Andriacchi and Favre, 2014; Creaby et al., 2013).

In the knee joint, the thickness and mechanical properties of the articular cartilage varies in different regions of the joint as a result of different loadings experienced in each joint region. For example, the thickest cartilage in the knee joint is in the load-bearing areas of the tibiofemoral articulation (medial compartments), which are the areas that are in contact during the stance phase of walking (Andriacchi et al., 2009). During walking, approximately 70-75% of the load passes to the medial knee compartment, making this compartment highly susceptible to the development of knee OA (Felson et al., 2000; Hsu et al., 1990; Schipplein and Andriacchi, 1991). Despite the fact that appropriate loading is necessary to maintain healthy joint tissue, it is widely accepted that high knee joint loads during walking are a key risk factor for initiating and accelerating knee OA (Andriacchi et al., 2015; Bennell et al., 2011). While it is possible to objectively estimate knee joint compartment loads using three-dimensional (3D) gait analysis to obtain knee joint moments (Kutzner et al., 2013; Thorp et al., 2006), no study has identified a specific threshold beyond which the magnitude of the joint moment becomes harmful.

In summary, whilst the precise pathophysiology of knee OA is highly complex and not clearly understood, all the above risk factors show that ***OA is a multifactorial disease, driven by mechanical factors within the context of systemic susceptibility***. Accordingly, a review paper by Andriacchi et al. (2015) developed a system model of the influence of the integrated behavior of various components (***biological, mechanical and structural***) on the capacity of cartilage to adapt to biomechanical change (maintaining healthy cartilage) and on the onset/development of OA (see Figure 2-5). The biological component included factors that influence cell metabolism, and the level of systemic inflammation and genetic etiologies.

Meanwhile, the mechanical component involved all biophysical signals (kinematic, kinetic and muscle functioning) that generate mechanical stimuli during ambulation, to the level of the local mechanical cell environment. Meanwhile, the structural component involved altered joint alignment, changes in bone structure, and changes in cartilage thickness/shape properties. Hence, this model suggests that a healthy articular joint will be maintained and become conditioned to any change, as long as each of the components operates within a normal range (see Figure 25b). However, mechanical changes (in the context of biological susceptibility) seem to be commonly associated with most of the risk factors that appear, prior to the development of clinical OA (Andriacchi et al., 2015). They often occur with metabolic changes (to bone and soft tissue) and changes in levels of inflammatory substances (Andriacchi et al., 2015; Sanchez-Adams et al., 2014). The interaction between these biological and mechanical changes will determine the clinical progression of OA (Andriacchi et al., 2015). Therefore, understanding these components will help to detect any deviations from normal ranges and to assess the risk of developing clinical OA.

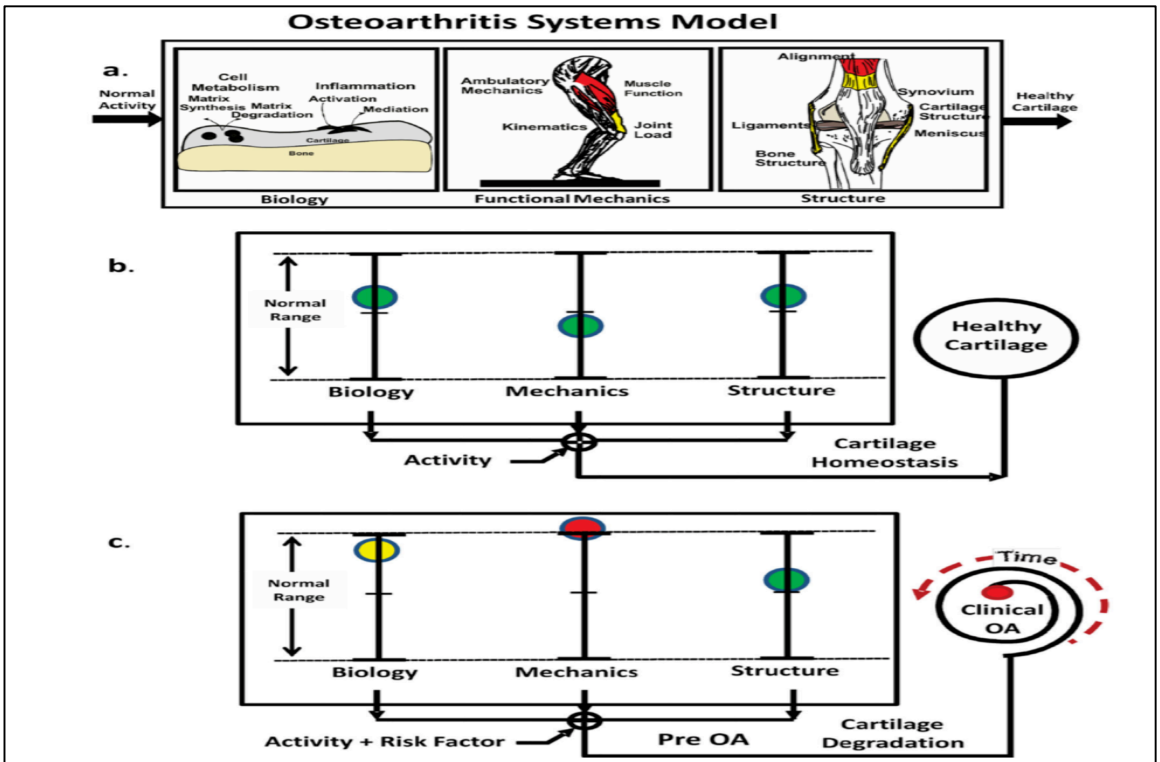


Figure 1.
The OA systems model (a) considers cartilage health to be dependent on the integrated behavior of biological, mechanical and structural components where healthy homeostasis (b) is maintained when each of the components is within normal ranges during normal activity. Introducing a "Risk Factor" moves the system out of homeostasis (c). For example (c), if the " Mechanics" component (red) moves out of normal range then cartilage will begin to degrade (Pre OA) and the "Time" to develop "Clinical OA" will depend the state of the other components.

Figure 2-5: The OA systems model of the integrated behaviour of biological, mechanical and structural components of the disease Adapted from (Andriacchi et al., 2015).

2.4 Measuring Knee Joint Load

An objective measurement, reflecting the nature of load and compression on the knee joint during activities such as walking is needed to assess the risk of OA. Using 3D gait analysis (an inverse dynamic approach) as a non-invasive measure will help to quantify the external stresses (moments) on the knee joint and provide a good indication of dynamic compression load (Amin et al., 2004). In addition, it will assist in developing effective methods to reduce load and the potential risk of OA. External knee joint moments (reflected by KAM and KFM) are used as surrogate measures of loading, with established associations between increased peak KAM and KFM, and heightened risk of developing OA (Chehab et al., 2014; Creaby et al., 2013; Thorp et al., 2006).

2.4.1 Knee Adduction Moment (KAM)

Over the past 20 years, KAM has been of particular interest as a surrogate gait analysis measure for medial knee loading (T. Miyazaki et al., 2002; Sharma et al., 1998). It has been shown to be a reliable and valid alternative measure for directing contact force measurement for loading and is commonly used to evaluate the effect of biomechanical factors on the progression of knee OA, using 3D motion analysis (Birmingham et al., 2007; T Miyazaki et al., 2002). KAM is defined as the rotatory force (in the frontal plane) that tends to adduct the knee joint. It is calculated as the product of the ground reaction force (GRF) that passes medially to the knee joint and the perpendicular distance of this force, i.e. the moment arm from the centre of the knee joint (see Figure 2-6) (Thorp et al., 2006).

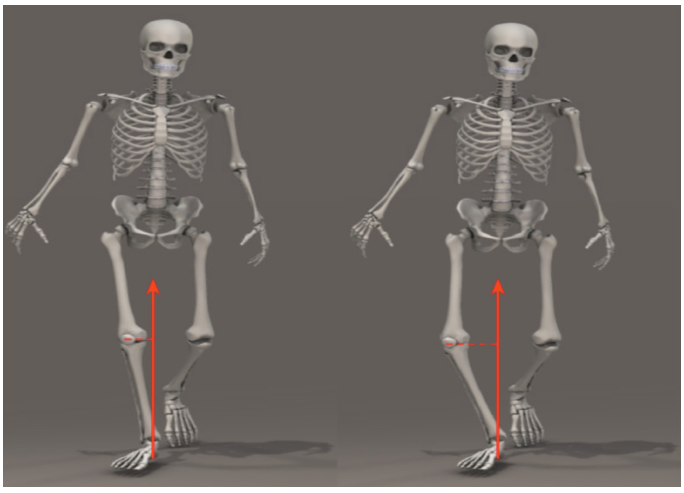


Figure 2-6: Knee adduction moment principal components (GRF and moment arm). High knee moment arm (right) (Levinger et al., 2013)

In 3D gait analysis, the KAM waveform is characterised by two peaks (the maximum magnitude at a single time point of the stance phase) during the stance phase of walking and one trough (see Figure 2-7) (Newell et al., 2008). However, the timing and magnitude of the two peaks, relative to one another, can vary considerably. According to (Thorp et al., 2006), the KAM peaks are located at the mid-stance for the first peak (frequently the largest peak) and at the terminal stance for the second peak. However, Newell et al. (2008) reported that the first KAM peak appears at 15% of the gait cycle and the second peak, at 45%; while the mid-stance trough occurs at 30% of the gait cycle. This makes it difficult to identify a single summary measure of the risk of OA, based on the features of time-varying KAM.

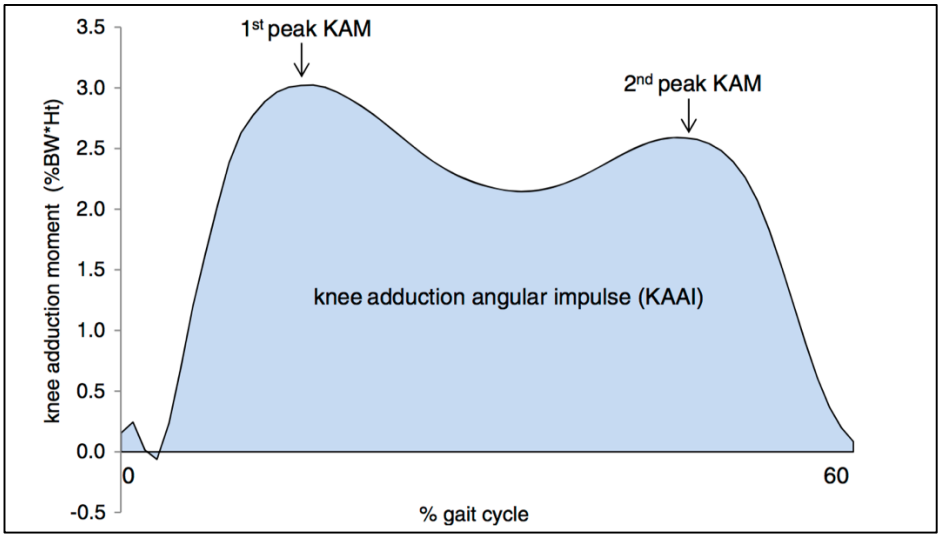


Figure 2-7: KAM waveform (peaks and impulse) (Levinger et al., 2013)

Different studies have shown the relationship between KAM and the existence and progression of OA. According to a longitudinal study by (Amin et al., 2004), in participants with no history of knee joint symptoms at baseline motion analysis, those with a high KAM peak developed future chronic knee pain. In another longitudinal study (T Miyazaki et al., 2002), the KAM value at baseline was found to predict radiographic OA progression in the medial compartment of the knee joint over time. The result of the above study showed that a 1% increase in KAM increased the risk of radiographic OA progressing in the knee by 6.64. Likewise, Morgenroth et al. (2014) found significant correlations between medial tibiofemoral joint degeneration and KAM peak, and between KAM loading rate and KAM rate magnitude. Common across all of these studies is the reliability of some aspect of KAM as an indicator of medial compartment compressive loading during walking, and it has been shown to be an

important predictor of the presence, severity and progression of radiographic knee OA (Morgenroth et al., 2014). However, despite peak KAM being an important method of calculating knee joint load, it measures the load at the maximum value of the curve during stance and does not consider the duration. For instance, load duration will be different between high and low walking speeds (since slow speeds increase stance time).

Accordingly, many studies utilise the peak over the whole stance, specify the magnitudes of both peaks, or attempt to capture the nature of the entire KAM profile using the impulse (Bennell et al., 2011; Kean et al., 2012; Thorp et al., 2006)). Therefore, recently, the total area under the KAM curve created by the KAM impulse has been shown to be strongly related to structural changes to OA in response to the duration of the stance time. Thorp et al. (2006) are considered to be the first to use KAM impulse to measure knee load in individuals with OA; finding that, compared to KAM peak, KAM impulse is the only measurement to reveal a significant difference between mild and moderate OA. Moreover, Bennell et al. (2011) and (Kean et al., 2012) found that the relationship between KAM impulse and cartilage loss was stronger than for KAM peak. Furthermore, they reported that compared to KAM peak, KAM impulse gives more comprehensive information on the medial compartment's joint load. However, despite the fact that both the impulse and peak measures have been considered as valuable for predicting OA development and progression, KAM impulse provides more comprehensive information on medial knee joint loading (integrating both magnitude of load and duration of stance) (see Figure 2-7).

2.4.2 Knee Flexion Moment (KFM)

As reported earlier, KFM is an indirect proxy measurement of external load on knee joint compartments, as well as of KAM. Similar to KAM, KFM is primarily determined by the magnitude of the vertical GRF and the moment arm to the knee joint centre on the sagittal plane (Derrick, 2004; Ho et al., 2012). Knee RoM has a leading role in directing knee flexion and extension moments during walking, because it increases and decreases the moment arm of the GRF in relation to the joint centre (Creaby et al., 2013; Derrick, 2004; Ho et al., 2012). At heel strike, vertical GRF passes anteriorly to the knee joint, generating an extension moment. As the limb is loaded during stance, the vertical GRF gradually moves towards the centre of the knee joint and continues moving at the back of the knee, creating the first KFM

peak at early stance. As the body moves forward, knee flexion RoM progressively decreases and reaches full extension, creating another knee extension moment at mid-stance. The subsequent increase in knee RoM will then create the second KFM peak at the late stance phase (see Figure 2-8) (Perry et al., 1992).

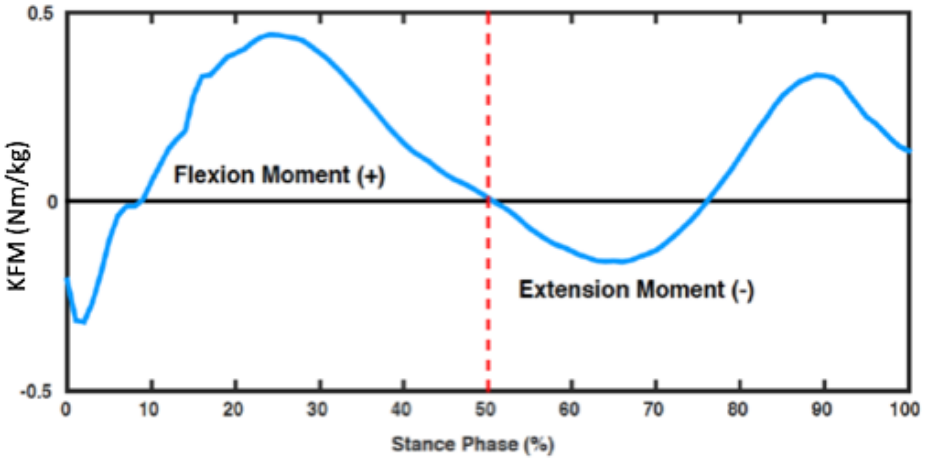


Figure 2-8: Knee flexion moment waveform (adapted from (Perry et al., 1992)

Compared to KAM, KFM has received less attention in the literature, but it has recently been found important in knee joint loading and OA (Manal et al., 2015). Higher KFM is suggested as contributing to increased knee joint contact force (Manal et al., 2015; Walter et al., 2010)), presence (Teng et al., 2015), and increased symptoms and disease progression (Chehab et al., 2014; Creaby et al., 2013; Farrokhi et al., 2015) of knee joint OA.

According to Manal et al. (2015), high peak KFM is an important predictor of medial compartment contact force, as, compared to KAM, KFM improves the predication of contact force by 22%. However, the above authors advise that both KFM and KAM should be considered when trying to assess the amount of, and/or change in, joint contact force. This finding supports previous work by Walter et al. (2010), who referred to the role of KFM, along with KAM, in high knee joint contact force and its contribution to medial knee joint load.

Compared to individuals with no OA, high KFM has been found to be associated with the presence of patellofemoral OA. A recent study by Teng et al. (2015) explored the associated biomechanical factors in individuals with isolated patellofemoral joint OA, compared to a control group with no symptoms of knee joint OA. By using MRI and 3D gait analysis, the study

results showed that individuals with patellofemoral joint OA (with articular cartilage lesion on MRI) presented with 33% higher peak KFM and 53-57% greater KFM impulse in the second half of the stance phase. Moreover, many studies have shown the association between different factors, such as knee flexion ROM/excursion and quadriceps muscle activation, with the alteration of KFM and its role in increasing knee OA symptoms and disease progression (Chehab et al., 2014; Creaby et al., 2013; Farrokhi et al., 2015) (see Figure 2-9).

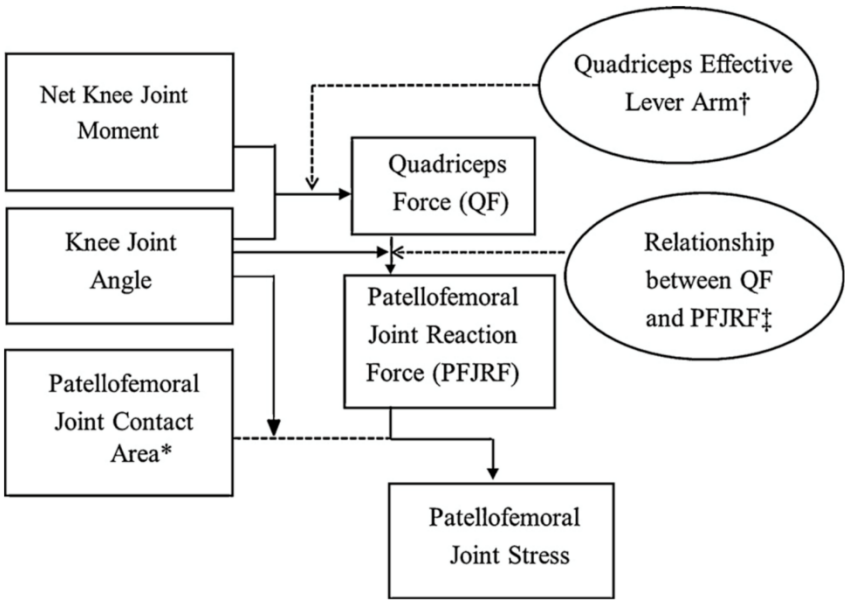


Figure 2-9: Flowchart of patellofemoral joint stress quantification model (adapted from (Ho et al., 2012)

2.4.3 Factors Altering Knee Joint Load

As reported earlier, external knee joint moment is estimated according to the vector of GRF and the moment arm from the centre of the rotation (knee joint) and GRF. Manipulating these two components is considered to be pivotal to altering knee joint moment. Therefore, many factors have been found to be associated with different gait patterns that shift knee joint loads on both the sagittal and frontal planes.

2.4.3.1 Knee Adduction Moment (KAM)

As the measurement of KAM is principally determined by the product of GRF and moment arm to estimate external adduction loads, the following biomechanical factors, measured using motion analysis systems, have arguably received most attention in recent years, mainly

in relation to the proposed association with altered joint moments and knee OA (Simic et al., 2011; Simic et al., 2013; Telfer et al., 2017).

Walking Speed

Altered walking speed is considered to be one of the main factors associated with knee joint load during walking. It has been claimed that an increase or decrease in walking speed has the biggest effect on KAM, because of mechanical changes, both kinetic (GRF and muscle action) and kinematic (ROM), which occur to body mass and the duration of stance time (i.e. increasing or decreasing the duration of the knee joint's exposure to load) (Robbins and Maly, 2009; Telfer et al., 2017). In contrast, the relationship between self-selected speed and KAM features has produced some conflicting findings, as KAM has been found to be either weakly or positively correlated with self-selected speed in different populations (Hunt et al., 2008; Thorp et al., 2006).

Robbins and Maly (2009) explored changes in KAM measures (peaks and impulse) for a group of healthy individuals, walking at different speeds. KAM measures were compared after the participants had walked at three different speeds: self-selected speed (SS), fast speed (15% more than SS), and low speed (15% less than SS). The results showed a significant increase of peak KAM at the fast speed, when compared to the lower walking speeds; while KAM impulse showed a greater significant increase at slow speed, compared to the SS and fast speeds. These results are supported by numerous studies (Ardestani et al., 2016; de David et al., 2015; Khan et al., 2017; McClelland et al., 2010; Telfer et al., 2017; van den Noort et al., 2013; Zeni and Higginson, 2009) that have showed an increase in peak KAM with accelerated walking speed in healthy individuals. This provides evidence of the association between altered walking speed and the properties of KAM. In contrast, Landry et al. (2007) revealed that an increase in the walking speed of a healthy group did not make any significant change to the overall magnitude of KAM; in fact, it led to a reduction in the KAM value during the late stance phase. However, compared to previous studies, the SS walking speed of the participants in the above study was already high (1.4m/s), which may mean that the difference in KAM compared to the higher speed is insignificant.

In other populations (those with pathological gait, such as OA), the influence of walking speed on KAM measures (i.e. peaks and impulse) varies between studies and between different disease stages (Astephen Wilson, 2012; Landry et al., 2007; Mundermann et al., 2004; Zeni and Higginson, 2009). Therefore, it is widely believed that one of the main problems involved in interpreting the pathology of gait variables for groups of participants consists of differences in other related variables, such as walking speed (Astephen Wilson, 2012).

Mundermann et al. (2004) conducted a study that investigated the relationship between SS walking speed and peak KAM in a group (n=44) with knee OA of varying disease severity (as assessed using Kellgren/Lawrence grades). They found that the severity of the knee joint OA influenced the KAM-walking speed relationship slops, as they were significantly greater in those with less severe knee OA, compared to the asymptomatic control participants. Accordingly, the above study concluded that slowing the walking speed is a potential method of reducing load (KAM) in a subject with OA. However, this study looked only at a cross-section of SS walking speeds and did not investigate the differences at increased, decreased or control walking speeds. Meanwhile, Landry et al. (2007) examined the biomechanical features characterising the gait of healthy (n=43) and moderate knee OA (n=41) groups, ambulating at SS and fast speeds (130% of the SS speed). Their results revealed that peak KAM in the OA group increased with an acceleration in walking speed, indicating that peak KAM was affected by speed, but not the severity of the OA. In contrast, the result of the KAM waveform was not affected by walking speed, but was higher in the OA group. Another study, by Zeni and Higginson (2009), investigated the effect of different walking speeds (at 1.0 m/s, SS and fast walking speeds) on KAM, with varying severity of knee OA (moderate OA n=21; severe OA n=13). However, at the control walking speed (1.0 m/s), peak KAM did not significantly differ between the moderate and severe OA groups. Moreover, while the moderate OA group presented with increased peak KAM, subjects with severe OA showed no significant difference in peak KAM at SS and a fast walking speed. These variations between studies limit the possibility of drawing consistent conclusions about the relationship between gait speed and KAM in an OA population, because of the additional factors that influence KAM.

Changes in walking speeds among different populations is not the only factor that modifies KAM features, given that the presence of other factors, such as foot progression (van den Noort et al., 2013), pelvic obliquity (Chang et al., 2005), trunk lean (Simic et al., 2012), and stride length (Allet et al., 2011; Russell et al., 2010) may contribute to contradictory findings between studies (Simic et al., 2011).

However, despite the potential effect of different walking speeds on KAM, the relationship between KAM and very slow walking speed is not yet clear. To the best of our knowledge, however, most of the studies conducted to date have used walking speeds of over 1.0 m/s. Therefore, more research needs to be carried out on healthy participants to account for the influence of very slow walking speeds.

Pelvic Obliquity

Pelvic obliquity (lateral pelvic tilt) is defined as the rotation angle of the pelvis in relation to the medio-lateral axis of the horizontal plane, correlated with the height of the hip (Baker, 2001). The pelvis rotation angle from the start of walking until the end shows a gradual increase of tilting over the stance leg, reaching the maximum and creating the first peak at 23.1% of stance. The second peak, at 81.5% of stance, occurs when the pelvis reaches maximum tilt over the swing side (Hunt et al., 2008).

Pelvic movement patterns present in different ways in relation to their role in increasing or decreasing knee joint load. ***Pelvic drop*** is a biomechanical abnormality that occurs when the hip abduction moment (of the stance limb) decreases, due to a weakness in hip abductor muscle strength. As a result, it has been found that the contralateral pelvis (of the swing limb) drops and leads to a mechanical change in the knee by shifting the centre of mass (CoM) away from the stance limb and increasing the moment arm (i.e. excessive femoral adduction of the stance limb) (Chang et al., 2005) (see Figure 2-10). In contrast, ***pelvic rise/hike*** is used as an adaptive/compensatory strategy in different pathologies to fulfil certain functions (Stanhope et al., 2014a) or to reduce impairment (Hunt et al., 2010) while walking by shifting the CoM toward the stance limb and reducing the moment arm.

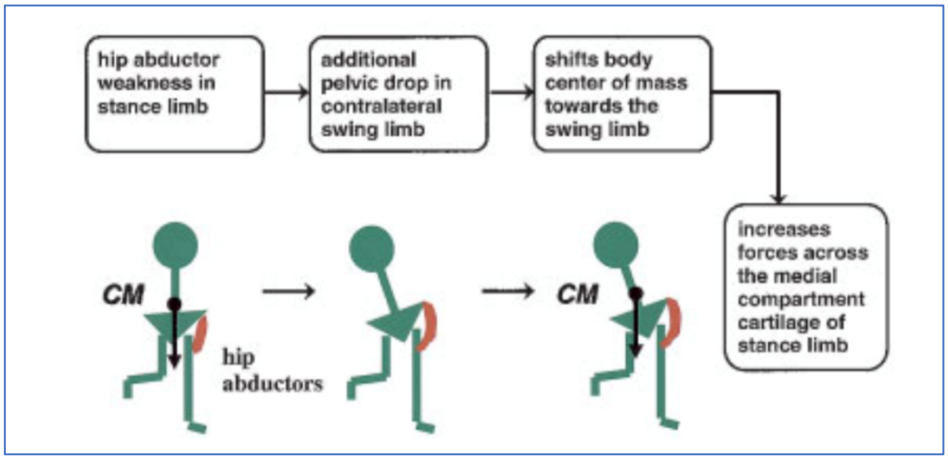


Figure 2-10: Pelvic drop mechanism and CoM shift (Chang et al., 2005)

The relationship between an increase in KAM and altered pelvic obliquity has been examined during stance on a single limb. Takacs and Hunt (2012) compared KAM in a healthy group, with regard to two pelvic conditions: at pelvic level position and at contralateral voluntary pelvic drop. The results showed a significant increase ($p=0.001$) of stance leg KAM (peak and impulse) with contralateral pelvic drop. However, all comparisons were conducted under different stance conditions and not during walking. The above authors suggested that the assessment of proximal biomechanics, such as pelvic obliquity, is very important in identifying and treating knee joint load. These results are supported by Dunphy et al. (2016), who investigated the effect of pelvic drop on KAM during walking. Fifteen healthy participants were asked to walk on a treadmill with a unilateral pelvic drop (contralateral to the stance leg), after creating the pelvic drop pattern during over-ground walking practice. Compared to the participants' typical gait pattern, the above result showed a significant increase in both KAM peak and impulse ($p<0.001$) measures in the stance leg. In addition, the pelvic drop showed a high correlation with changes in peak KAM ($r=0.85$) and KAM impulse ($r=0.88$).

Conversely, the pelvic rise/hike movement pattern has been correlated with pelvic kinematics and KAM magnitudes during walking. According to Hunt et al. (2010), the pelvic rise or hike of the swing limb contributes to trunk lean towards the stance limb (i.e. the contralateral side). In the above study, this adoptive mechanism was adapted by individuals with knee OA to reduce pain during walking. Therefore, a study by Bechard et al. (2012) showed that pelvic rise and lateral trunk lean are significantly higher ($p=0.01$ and $p=0.03$, respectively) in individuals with OA, compared to those without OA. This result is supported by Chiba et al.

(2016), who showed the correlation between high pelvic elevation during single leg standing and peak KAM. However, no study has investigated the effect of isolated pelvic rise patterns on the contralateral limb's knee joint load.

Trunk Lean

During walking, body posture (i.e. trunk lean) plays an important role in changing lower limb mechanics and joint load (Hunt et al., 2008). However, the relationship between trunk lean and knee joint load (i.e. KAM magnitude) has been found to vary, as it depends on the lateral trunk movement pattern (i.e. the direction and/or amount of lean) towards either the stance or swing limbs. In both situations, the mechanism of lateral trunk lean is to shift the CoM towards either the stance limb (reducing the moment arm) or swing limb (increasing the moment arm of the stance limb), thus increasing or decreasing subsequent KAM, respectively (Tanaka et al., 2008) (see Figure 2-11). According to Hunt et al. (2008), trunk lean is considered as the largest amount of variance in the KAM and, compared to other kinematic variables of gait, the amount of lateral trunk lean has the highest correlation with KAM peaks.

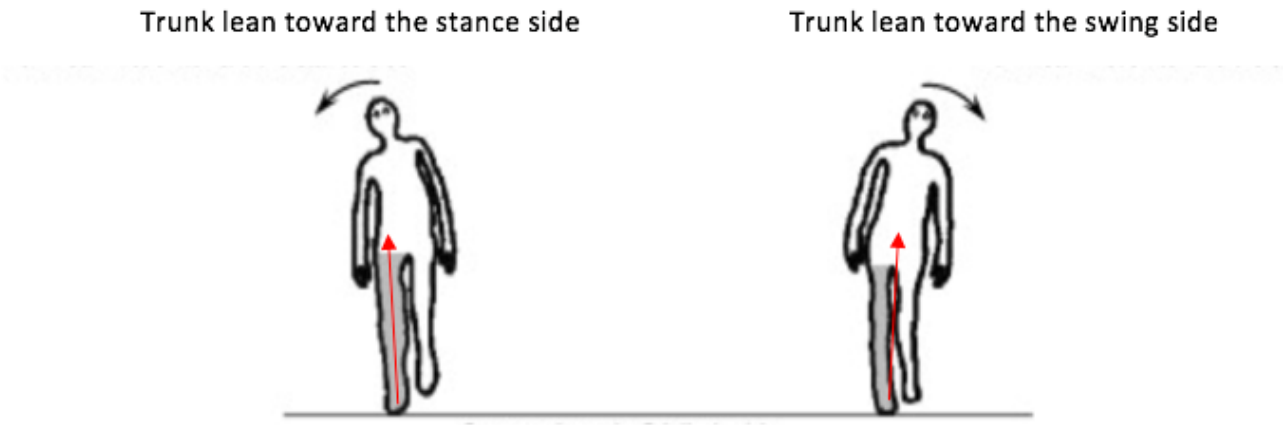


Figure 2-11: Lateral trunk lean directions (adapted from (Tanaka et al., 2008)

Leaning the trunk ***towards the swing side*** has been found to increase knee joint load and may increase the risk of knee OA. Takacs and Hunt (2012) explored the consequences of shifting CoM away from the stance limb (i.e. contralateral trunk lean towards the swing side) on knee joint load in a healthy group. The results of their study indicated that imposed contralateral trunk lean towards the swing side significantly increases knee moment arm ($p<0.001$) and KAM ($p<0.001$), compared to the natural trunk position. Despite all trials being performed

from single leg standing positions, this finding provides new evidence of the effect of mechanical changes in trunk lean towards the swing limb, and the subsequent CoM alteration to lower limb knee joint load (see Figure 2-12).

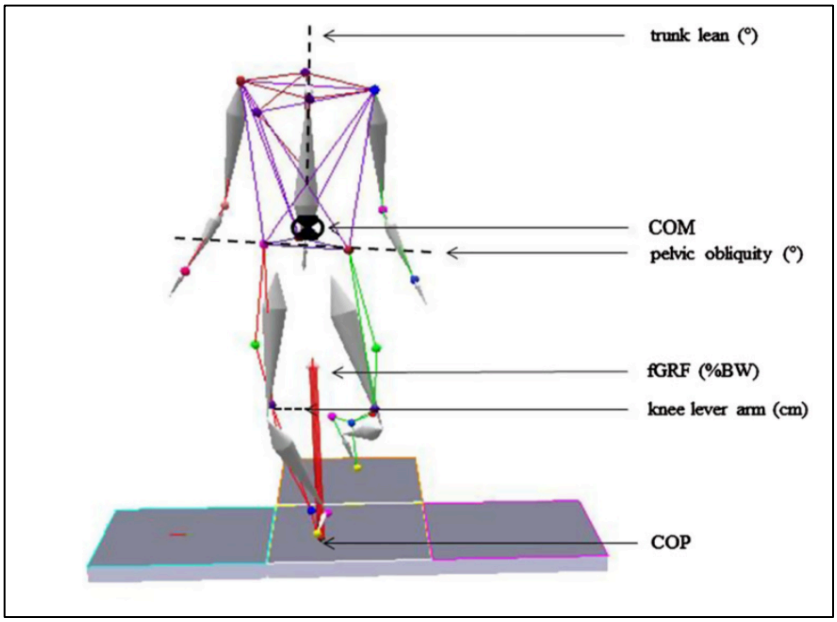


Figure 2-12: Trunk lean towards the swing limb (Takacs and Hunt, 2012)

In contrast, trunk lean ***towards the stance side*** was found to decrease the amount of KAM. One study by Hunt et al. (2011) examined the knee's biomechanical changes during walking, with increasing lateral trunk lean in young healthy individuals. Their result showed that an increase in trunk lean angle towards the stance limb reduces KAM significantly. The bigger the trunk lean angle, the greater the reduction in knee joint KAM. However, the fact that the sample was made up of young participants may have been the reason for achieving a successful significant reduction in KAM, due to their ability to achieve greater trunk lean (12° was the maximum target lean angle for the study). The reduction in knee joint load with trunk lean is supported by Gerbrands et al. (2014), who reported that, compared to normal walking, lateral trunk lean towards the stance limb during walking leads to the greatest reduction in KAM (both peaks and impulse) in healthy adults. However, all the data for their study were collected while the participants were barefoot, which reduces the study's generalisability.

In knee OA, trunk lean gait pattern towards the stance limb (i.e. the painful side – found to be the preferred gait pattern among individuals with OA (Hunt et al., 2010) – has been negatively correlated with the first and second peak of KAM (Hunt et al., 2008) and found to

be the most effective way of reducing KAM (peaks and impulse) in both early and late stance phases (Gerbrands et al., 2017). These findings show the influence of upper body lean on mechanical changes to the knee joint by reducing KAM.

Foot Progression

In normal walking, the foot position mainly points slightly outwards ***(toe-out***), as the foot progression angle is produced by external foot rotation with respect to the direction of the forward progression. However, in rare occasions or conditions, the foot points inward (***toe-in***), as the foot progression angle is internally rotated with respect to the line of walking (Simic et al., 2013) (see Figure 2-13). Both gait patterns, either toe-out or toe-in, are found to have an effect on lower limb joint load. Changing the foot position during gait moves the centre of pressure (CoP) and subsequent GRF vector location laterally (reducing the moment arm at toe-out) or medially (increasing the moment arm at toe-in). Accordingly, the joint moment of knee (KAM) will change (van den Noort et al., 2013).

The relationship between KAM and foot progression varies across medial compartments throughout the entire stance phase during walking. According to Simic et al. (2013), increasing the toe-out angle leads to an increase in early stance KAM (first peak) and a decrease in KAM impulse. This increase in first peak KAM has been supported by many studies (Khan et al., 2017; van den Noort et al., 2013). In contrast, toe-in shows an agreement in reducing first peak KAM (Khan et al., 2017; Shull et al., 2013; Simic et al., 2013; van den Noort et al., 2013). However, KAM impulse has generated contradictory results, given that it appeared to increase (Simic et al., 2013) with toe-in in some studies, while other studies reported a decrease (Khan et al., 2017). According to van den Noort et al. (2013), in addition to the role of toe-out in increasing KAM in early and mid-stance by 21-24%, toe-out reduces KAM in late stance by 56%. All these variations in study findings may be due to differences in walking speed (Khan et al., 2017) and the wide range of foot progression angles for toe-in (10°) and toe-out (up to 40°) (Simic et al., 2011; Simic et al., 2013). Moreover, despite the normal range of foot progression angles being reported as 5°, indicating toe-out (Shull et al., 2013), no study has identified the cut-off ratio for foot progression angle at which the range starts to account for an increase or decrease in KAM during walking.

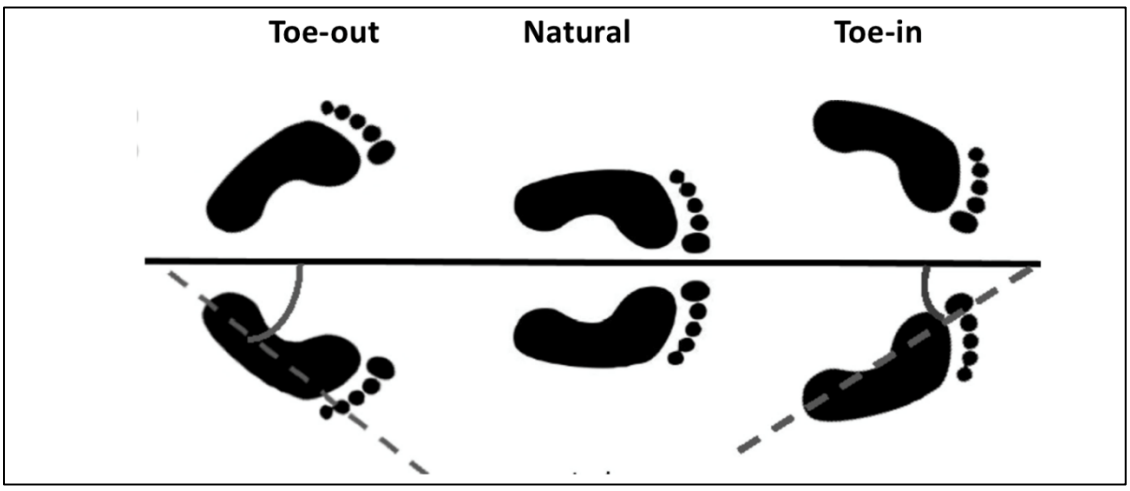


Figure 2-13: Foot progression (adapted from (Carr et al., 2016)

Stride Length

Stride length is one of the spatiotemporal parameters that play an important role in determining walking speed, gait pattern and kinematic changes (Ardestani et al., 2016; Danion et al., 2003). However, the role of stride length (or step length) on lower limb kinetics and on knee moments in particular has not been well established. Russell et al. (2010) investigated the effects of changing step length on KAM (peak and impulse) in two groups: obese women and a healthy control. The results indicated that decreasing step length by 15% reduces KAM impulse, while peak KAM showed no difference. However, these female participants only reduced walking speed by using a treadmill and the lack of body mass normalisation for joint moment factors may have contributed to this reduction. In one recent study, (Ardestani et al., 2016) explored the effect of stride length and cadence on the joint moment of the lower extremities and compared to increasing speed by cadence, an increase in walking speed by increasing step length was found to raise the knee joint moment on the frontal plane during early stance. However, to achieve the true effect of step length on joint moments, walking speed effect should be adjusted either by matching the speed or covariating it statistically.

2.4.3.2 Knee Flexion Moment (KFM)

Similar to KAM, KFM has been discussed as altered by numerous biomechanical factors. The following factors are arguably the biomechanical factors that have received most attention in estimating/altering joint flexion moment/load.

Walking Speed

Similar to the frontal plane, changing walking speed on the sagittal plane alters the knee joint flexion moment (KFM), because of the remarkable effect of speed on the sagittal plane joint motion and lever arm. In a study by van den Noort et al. (2013), the effect of different walking speeds on knee joint moment were investigated in a healthy group. The result showed that the KFM moment increases with the acceleration of walking speed. In addition, reduced walking speed results in a reduction in KFM during both early and late stance phases. Despite all the recruited participants being young adults (23.8 ± 3.9 years) in the above study, thus reducing its generalisability, these results align with those of many other studies on different populations (Ardestani et al., 2016; de David et al., 2015; Landry et al., 2007; Zeni and Higginson, 2009).

Knee Range of Motion (RoM)

The knee joint, as a weight-bearing joint, plays a fundamental role in walking, adapting to weight bearing and load distribution. According to Creaby et al. (2013), knee joint load on the sagittal plane is associated with altered knee joint flexion patterns. Theoretically, during walking, the knee flexion excursion during the early stance phase (from heel-strike to the peak of knee flexion) plays an important role in assisting shock absorption by means of gradual deceleration of the vertical velocity of the body's CoM, which consequently leads to reduced magnitude of the peak vertical GRF and joint moment (Derrick, 2004). However, many studies have shown that a decrease and/or increase in knee joint angle during stance may increase the risk of OA, due to an increase in contact force and KFM on the anterior knee compartment (Creaby et al., 2013; Farrokhi et al., 2015; Ho et al., 2012; O'Connell et al., 2016; Teng et al., 2015). Ho et al. (2012) showed that the greater the increase in knee flexion RoM, the greater the KFM and knee load that are primarily determined by moment arm and GRF magnitudes.

Muscle Contraction

As reported earlier, there are two main ways in which the knee distributes the load experienced during walking: through the external moments around the knee and through the contribution of muscles, ligaments and cartilage to support these moments (Creaby et al., 2013; Shelburne et al., 2006). Thus, numerous studies have illustrated the primary contribution of muscles in crossing the knee joint, made by the quadriceps, gastrocnemius

and hamstrings during early and late stance (Kim et al., 2009; Sasaki and Neptune, 2010). These muscles are activated in tandem (through co-contraction, in which agonist muscles counter antagonist muscle) to provide the required stability and load on the joints by generating the net internal moment (Heiden et al., 2009). During walking, the net external KFM reflects the different muscle activation pattern across the knee joint. Thus, any increase in KFM will increase the force produced by the quadriceps and heighten the compressive load on the anterior compartment of the knee joint (Winby et al., 2009).

In some specific knee joint impairments, such as weakness of the quadriceps, the presence of this impairment during stance will limit knee extension RoM and increase KFM, thus forcing the quadriceps to provide the required stability (Farrokhi et al., 2015; Ho et al., 2012).

Stride Length and Frequency

During walking, individuals use different strategies such as stride frequency (cadence) and/or step length to increase gait speed (Allet et al., 2011; Ardestani et al., 2016). However, these two methods may have an effect on the magnitude of KFM during walking. According to (Ardestani et al., 2016), who investigated the influence of these two strategies on KFM, individuals walking with an increased stride length showed an increase in KFM, compared to those walking with high cadence. The above study supports previous work by Allet et al. (2011) who showed the effect of altered stride length (based on five different imposed stride lengths: +20%, +10%, preferred, -10% and -20%) on knee joint moment during walking. The result showed that KFM is susceptible to step length alterations (as it increases and decreases in direct proportion to step length).

In pathological conditions associated with gait asymmetry such as amputation and unilateral OA (individuals who rely heavily on their sound limb), lower limb changes in joint moment, compensatory movement, and over/asymmetry loading between sides may play an important role in the development of OA in the (originally) non-affected limb, which can result in additive functional disability (N. Shakoor et al., 2002; Struyf et al., 2009; Lloyd et al., 2010; Jones et al., 2013; Morgenroth et al., 2014). The result of asymmetric moment/loading patterns when one limb is affected by disease/injury (for example, amputation or OA) is often the development of OA in the unaffected limb.

2.5 High Joint Moments during Gait in Unilateral Joint Conditions Linked to the Progression and Development of Osteoarthritis (OA)

2.5.1 Ambulatory Mechanics and Onset of Knee Osteoarthritis (OA)

As reported earlier, cyclic loading (as a mechanical stimulus) of the lower limb, which primarily occurs during walking, exerts force on the knee joint, estimated as 2-3 times the subject's body weight per step (Kutzner et al., 2010). Moreover, it has been suggested that the internal structures of the knee joint, such as cartilage, become conditioned to high cyclic ambulatory loads and as long as there are no deviations from the normal patterns of locomotion, the structures of the knee joint are maintained (Andriacchi et al., 2015). However, if the knee joint experiences a high load that is different from normal; for example, due to changes in kinematics under unilateral conditions (such as amputation or unilateral total hip and knee replacement (Shakoor et al., 2002; Shakoor et al., 2003) and in individuals with unilateral OA (Jones et al., 2013; Shakoor et al., 2014)), and the knee fails to adapt to this new load properly, the cumulative effects of repeated mechanical loading (with the presence of biological factors) could be pivotal to the development of stress-related knee injuries and disorders on the unaffected side. Alternatively, OA progression on the affected side may be increased (Andriacchi et al., 2015; Andriacchi et al., 2009; Andriacchi and Mündermann, 2006).

2.5.2 Unilateral Osteoarthritis (OA)

Individuals with unilateral OA have been found to be at high risk of developing OA in the contralateral knee joint (i.e. the knee of the opposite limb from the affected side), which supports the belief that asymmetric mechanical loading plays an important role in the development of knee OA (Andriacchi and Mündermann, 2006; Shakoor et al., 2003).

In a study conducted by Shakoor et al. (2002), it was shown that Individuals with a total unilateral joint replacement of the knee or hip are at heightened risk (almost 2.5 times) of developing OA in the contralateral side joints. To better understand the mechanisms of OA risk on the contralateral side joints in a unilateral total joint replacement, Shakoor et al. (2003) investigated whether increased risk of OA in the contralateral side knee was related to asymmetry in dynamic joint loading (i.e. a difference in peak KAM between limbs). Baseline

gait analyses were conducted on a number of participants before and after undergoing unilateral total hip replacement (THR). The results showed that the peak external knee moments were mostly higher on the contralateral knee, compared to the ipsilateral (same side) knee. In particular, KAM peaks and external knee extension moments were significantly different (i.e. increased in the contralateral side) after THR.

A recent gait analysis study carried out by (Jones et al., 2013) on individuals with unilateral knee OA demonstrated that 90% of those diagnosed with this condition developed radiographic changes on the originally non-affected side within 10 years. The above study results showed that the affected and unaffected knee joints of individuals with unilateral knee joint OA were exposed to a focal load distribution on the medial compartment, reflected in increased KAM peak, which was prone to increase pain in the affected side and increase the risk of the disease in the unaffected side knee joint (Jones et al., 2013). Recently, Shakoor et al. (2014) evaluated the relationship between the asymmetry of quadriceps muscle strength and joint proprioception in individuals with unilateral hip OA and joint loading. The above study found that asymmetry in these factors between limbs coincided with a significant 10% increase ($p=0.029$) in peak KAM for the contralateral knee, compared to the ipsilateral side. These results illustrate a possible future risk of OA in the contralateral knee joint, due to neuromuscular asymmetry in the unilateral OA population.

2.5.3 Amputee Populations

Similar to the finding that individuals with unilateral OA are at heightened risk of developing bilateral disease, research has also identified this trend in long-term traumatic lower-limb amputees. People with unilateral amputation are at risk of a number of secondary musculoskeletal impairments, such as lower limb joint pain and OA of the intact limb joints (C. B. Robbins et al., 2009). Knee pain prevalence among amputees was found to be 40%, compared to 20% in non-amputees. Furthermore, the knee of the intact limb was 3.3 times more likely to develop pain and OA. This finding is supported by Struyf et al. (2009), who explored the prevalence of knee and hip OA in the intact leg amongst traumatic leg amputees, compared with a healthy population. They found that the prevalence of knee OA was 27% (men 28.3%; women 22.2%) and hip OA was 14% (men 15.3%; women 11.1%) higher, compared with healthy control participants (knee OA: men 1.58% and women 1.33%; hip OA:

men 1.13% and women 0.98%). These rates demonstrate that unilateral amputees are almost 17 times more likely to develop knee OA in the sound limb, compared to age-matched non-amputees.

Gait asymmetry in individuals with unilateral amputation is a compensatory mechanism relating to the biomechanical adaptation of the function that is missing from the prosthetic leg. Compensatory gait asymmetry, particularly in spatiotemporal (time and distance), kinetic and kinematic parameters, and walking speed were found, relative to non-amputees, to increase the risk of knee OA in the intact leg, due to increasing mechanical load on the joint (Nolan and Lees, 2000; Nolan et al., 2003; Schaarschmidt et al., 2012). In individuals with unilateral amputation, gait spatiotemporal parameters between limbs are highly asymmetrical (Sagawa Jr et al., 2011). Isakov et al. (2000) found that the intact leg's spatiotemporal parameters showed a significant increase in stance time and single support time, while swing time and step length parameters were shorter, compared to the amputated leg. Nolan et al. (2003) studied the impact of temporal asymmetry on the increase in joint load among individuals with unilateral amputation. Their study revealed that temporal asymmetry is responsible for increased GRF on the intact leg; resulting in greater joint loading. Therefore, increased knee joint load in the intact leg is a result of compensatory gait asymmetry, which may initiate the risk of knee OA (Andriacchi and Mündermann, 2006).

In addition to parameters of spatiotemporal symmetry, KAM has been shown to be asymmetrical between limbs in individuals with unilateral amputation. According to Royer and Wasilewski (2006), who explored the frontal plane moment in individuals with unilateral trans-tibial amputation, the intact limb's KAM peak was significantly higher when compared to the prosthetic limb (mean ±SD 0.55 ± 0.18 Nm/kg and 0.38 ± 0.22 Nm/kg, respectively). Despite the small sample size (n=10) in the above study and the fact that there was no control group to compare with, the results showed greater loads on the intact limb, potentially increasing the risk of developing knee OA on this side. KAM asymmetry was also reported by Lloyd et al. (2010), who investigated the relationship between muscle strength asymmetry and gait variable asymmetry, associated with risk of OA in the intact limb of trans-tibial amputees. Their results demonstrated that asymmetric knee extension strength is significantly related to asymmetry in KAM load rate (rho=0.714), and that asymmetric knee

flexion strength is moderately related to vertical GRF in the intact limb (rho=0.643). The literature demonstrates that asymmetry between limbs (for temporal, spatial and kinetic gait parameters) amongst unilateral amputees plays a fundamental role in gait compensation mechanisms, which puts individuals who rely heavily on their intact limb at risk of increased joint loading.

2.5.4 Stroke and the Risk of Osteoarthritis (OA)

Gait dysfunction (hemiplegic gait) is one of the main deficits among stroke survivors that limits their independence and participation. It leads to asymmetry in spatiotemporal, kinematic and kinetic gait parameters between the affected and unaffected limbs (Patterson et al., 2008). Consequently, it has been hypothesised that gait asymmetry is connected to numerous potentially undesirable issues, such as challenges to balance control, increased energy expenditure, increased risk of musculoskeletal injury to the non-paretic lower extremities, and reduced overall activity (Patterson et al., 2008).

Stroke is a condition that mainly affects individuals suffering from obesity, or else develops with increasing age. Therefore, these are risk factors that overlap the risk of developing OA; leaving subjects with lasting asymmetry in their gait (Zhang and Jordan, 2010). In addition, neuromuscular changes and muscle weakness (Rudolph et al., 2007; Shakoor et al., 2014), which are key impairments in stroke, have all been linked with OA. These factors contribute to abnormal kinematics, the repetition of high joint loads (Andriacchi and Mündermann, 2006), and inter-limb asymmetry in kinetic variables, which can increase pain and the risk of the disease developing in the knee joint on either side of the body (Jones et al., 2013). However, with age, an increase in body weight, and the influence of biomechanical changes (such as a mechanical stimulus) after stroke, will make stroke survivors vulnerable to knee joint OA.

The prevalence of obesity has been reported to be higher amongst stroke survivors. According to a mortality study by Towfighi and Ovbiagele (2009), 64.3% of stroke survivors are likely to be overweight/obese (based on the BMI$\geq$25 Kg/m^2). This increase in BMI may work as a potential barrier to long-term post-stroke motor and functional recovery (Sheffler et al., 2012). In addition, a secondary data analysis study by (Sheffler et al., 2014) investigated the

relationship between BMI and selected gait parameters (spatiotemporal, kinematic and kinetic) in chronic stroke survivors (n=108). After controlling for the effect of age, gender, stroke type, motor impairment level and walking speed, the results showed that BMI was positively associated with peak hip abduction angle in the non-paretic side, as well as step width. In contrast, BMI was negatively associated with the paretic side of both variables in ankle dorsiflexion at initial contact, and peak ankle power at push-off. Nevertheless, despite the above study investigating the influence of obesity on post-stroke gait, it remains unclear whether the impact of high body weight on the joints of the lower limbs, such as the knee joint, initiate/develop musculoskeletal comorbidities.

Aside from this and as reported earlier, age is considered to be an important risk factor of joint OA. Strokes can occur at any age, but the prevalence of injury clearly increases with age. According to Marini et al. (2001), after the age of 55, the risk of stroke almost doubles every 10 years. Therefore, OA can be considered as a comorbid pathology in stroke patients, because its prevalence increases with age.

More and more people are surviving strokes and living longer with persistent effects on walking with a hemiplegic gait pattern (Boysen et al., 2009). This interaction of walking impairments alongside the biologic changes occurring with age and obesity, there is potentially a heightened risk of developing comorbid OA over the longer-term. Irrespective of this, very few studies have investigated the development of OA as a comorbidity in the stroke population, although they share the same risk factors. In a recent cross-sectional survey study conducted to explore the prevalence of arthritis in a community-dwelling sample with (n=1892) and without stroke (n=1892), the results highlighted a slight increase in comorbid arthritis in the stroke group, with 53% of the stroke survivors suffering from arthritis, compared to the control group (43%). Moreover, a greater proportion of stroke survivors who were older and had high BMI reported lower limb arthritis, compared to those with stroke alone (Patterson and Sibley, 2016). That said, the above study has a number of limitations, including the fact that the findings failed to determine whether the arthritis appeared pre- or post-stroke. In addition, the study did not specify which joints/sides were affected by OA. Apart from this study, most other research on the links between stroke and knee OA have all examined whether individuals with knee OA are at subsequent risk of stroke

(Ong et al., 2013; Rahman et al., 2013a; Rahman et al., 2013b), or the negative effect of pre-existing OA on stroke survivors' potential rehabilitation and functional outcomes (Doruk, 2013; Nguyen-Oghalai et al., 2005).

Survey studies by Rahman et al. (2013a; 2013b) reported that people with pre-existing OA are at no greater risk of stroke than those without OA. These results are consistent with the findings of Ong et al. (2013), who also state that stroke is not associated with OA. However, pre-existing OA extends hospital stays (Ngueyen-Oghalai et al., 2005) and limits rehabilitation outcomes (Doruk, 2013) for OA individuals who suffer a stroke. Nevertheless, there are no studies examining whether persistent gait impairments, resulting from stroke, lead to the subsequent development of OA (as opposed to pre-existing OA leading to stroke). Understanding the relationship between stroke and OA can be helpful in an individual's long-term care and may assist in exploring possible early preventative interventions in the development of OA, so as to improve stroke survivors' quality of life.

The prevalence of post-stroke musculoskeletal symptoms, especially joint pain, are common and may increase functional limitations and delay recovery, as well as restricting stroke survivors' participation in daily activities following rehabilitation. A prospective cohort study on 327 stroke survivors from different centres showed that 32.4% of the individuals complained of musculoskeletal pain, with knee pain being the second most common type of pain after the shoulder joint (Kuptniratsaikul et al., 2009). However, the results did not indicate which side was more affected by pain. A self-report survey study by Hettiarachchi et al. (2011) showed that, compared with individuals in the general population, stroke survivors' joint symptoms were higher over the age of 55. Their results demonstrate that almost 50% of stroke survivors suffer from joint pain, with the knee being the most commonly reported symptomatic joint. However, the above study methods were limited by a lack of objective tests to identify whether self-reported pain after stroke was due to joint pathology or the result of neurological impairments.

Characteristic impairments of gait following stroke could lead to increases in KAM and KFM, which are indicative of OA risk. Specifically, changes to KAM and KFM following stroke can result from a slower walking speed (increasing KAM impulse with increased stance time) (Kim and Eng, 2004; Robbins and Maly, 2009), altered knee joint RoM and muscle co-activation

(increasing patellofemoral joint reaction forces) (Buurke et al., 2008; Chen et al., 2005; Creaby et al., 2013; Farrokhi et al., 2015; Hutin et al., 2012; Kim and Eng, 2004; B. Raja et al., 2012), and asymmetrical knee joint kinetic (moment) profiles between paretic and non-paretic limbs (Allen et al., 2011; Kim and Eng, 2003, 2004; Patterson et al., 2014; Teixeira-Salmela et al., 2001). Additionally, compensatory gait patterns that are common after stroke, such as hip hiking (altering the frontal knee moment arm due to ipsilateral pelvic obliquity and contralateral pelvic drop) (Chen et al., 2005; Chiba et al., 2016; Dunphy et al., 2016; Linley et al., 2010; Stanhope et al., 2014a), increased trunk lean (Van Criekinge et al., 2017), and toe-out and toe-in (Lamontagne et al., 2007; Shull et al., 2013), are also known to contribute to changes to knee joint moments during walking (Shull et al., 2013). Knee joint internal structures must adapt to these potential changes in joint load, in order to prevent joint degeneration. Studies have reported increased pain (Hettiarachchi et al., 2011) and reduced femoral cartilage thickness on stroke survivors' paretic side, compared to healthy individuals (Tunc et al., 2012), suggesting that following stroke, tissues may not adapt well to changes in joint load. However, the cause of pain and cartilaginous changes has not yet been identified, as a period of at least two years is required to observe the long-term effects of gait impairment on joint tissues and structures (Yang et al., 2005). Furthermore, studies that characterise knee joint loading over long-term stroke recovery are lacking. Overall, there is a dearth of understanding, regarding whether or not compensatory gait patterns (and hence knee joint loads) change over time after a stroke and the response of internal joint structures to any such change.

Despite the plethora of possible stroke-related biomechanical contributors to the development of knee OA, very few studies have investigated whether or not gait impairments following stroke alter joint moments (KAM and KFM) in a way that is known to indicate the risk of joint degeneration, or how these moments change (or not) over long-term recovery. A preliminary study on nine participants demonstrated that the measurement of limb-loading during gait is feasible after stroke (Marrocco et al., 2016). The above study revealed that despite the fact that the knee moment was not compared statistically between the stroke sides, mean KAM and KFM were comparable and showed no significant difference between sides, compared to healthy participants. However, there was high variability of peak KAM and KFM in the stroke survivors studied, with some exhibiting higher moments on the paretic side

and others, on the non-paretic side. Analysed on an individual basis, post-hoc single-sample t-tests revealed greater loading in the stroke participants on the paretic side (n=3), non-paretic side (n=1), and both legs (n=2), compared to healthy adults (Marrocco et al., 2016).
As a result of the variability between stroke survivors, it therefore remains unknown whether gait impairments following stroke alter joint moments in such a way as to increase the risk of developing comorbid knee joint OA. However, the major limitations of the above-mentioned study consist of the difference between the control and stroke survivors' walking speeds, which altered the joint moment properties (de David et al., 2015; Robbins and Maly, 2009) and, in relation to this, the use of peak moments instead of impulse. Additionally, the range of gait impairments and spatiotemporal asymmetries in stroke survivors is known to be vast (Sheffler and Chae, 2015). Moreover, despite the fact that the normality of distribution was not reported in this study, the decision to use a statistical test (a paired t-test) was not justified. Lastly, the study did not statistically compare the paretic and non-paretic sides. Therefore, the available studies on relatively small samples limit generalisability and make few reliable estimates of variability in heterogeneous populations of stroke survivors.

Clinically, a definitive understanding of the presence of loading patterns known to be risk factors for the development of knee OA following stroke is important, because this could help clinicians prioritise gait rehabilitation goals, in order to limit potential knee joint wear and tear in the longer term.

2.5.4.1 Negative Influence of Comorbid Conditions after Stroke

Functional limitation is one of the primary manifestations that creates difficulties for individuals with stroke in performing the activities of daily living (Beyaert et al., 2015). Therefore, improving mobility, especially walking independently, is one of the major goals for individuals with stroke (Winstein et al., 2016). Stroke survivors are vulnerable to many comorbidities as a result of the pathology itself or secondary to the disability caused by the stroke (Kuptniratsaikul et al., 2009). As reported earlier, musculoskeletal pain is common among stroke survivors, especially in the knee joint (Hettiarachchi et al., 2011; Karatepe et al., 2008; Kuptniratsaikul et al., 2009), which may be due to inter-limb asymmetry impairments between limbs (Patterson et al., 2014). Additionally, there is high prevalence of comorbid knee OA in stroke survivors, compared to healthy subjects (Patterson and Sibley,

2016). The presence of such comorbidity is reported to increase length of hospital stays (Nguyen-Oghalai et al., 2005), limit rehabilitation outcomes, and interfere with individuals' participation in rehabilitation programmes (Doruk, 2013). However, early diagnosis, prevention, and the provision of proper interventions for such morbidity may help to avoid any further complications and enhance the speed of recovery. Therefore, this current study explores the impact of lower limb asymmetry on knee joint biomechanics, especially mechanical loading, by quantifying knee joint load and exploring the potential risk of knee OA.

2.6 The Gap in the Literature

The most common impairment in walking after stroke is spatiotemporal asymmetry. Gait asymmetry limits functional mobility, which may be linked to the fact that individuals with stroke have increased joint symptoms, such as pain, compared to the general population. Research into conditions such as amputation and unilateral OA has shown that asymmetry in walking (as a fundamental mechanical stimulus of OA in the context of biological susceptibility) can lead to the development of musculoskeletal injury and/or disease in the non-affected limb. Specifically, KAM values (peak and impulse) and KFM throughout the stance phase of gait have been shown to be a key risk factor for the development of knee OA. In stroke, it has been hypothesised that stroke survivors' gait patterns contribute to an increased risk of joint degeneration. Thus, while we know a great deal about spatiotemporal asymmetries following stroke, we have relatively little knowledge about kinetic asymmetries, particularly those relating to KAM and KFM. These kinetic asymmetries may indicate a biomechanical mechanism for the development of comorbid OA, since they share the same primary risk factors, namely increasing age and BMI. In fact, to date, only one study (Marrocco et al., 2016) has published data on knee mechanics and load pattern in stroke populations in the context of the risk of secondary joint pain and degeneration.

Nevertheless, it is important to determine whether there are biomechanical risk factors for the development of OA **after** stroke, given that studies have shown that the pre-existence of OA limits the potential for rehabilitation and recovery amongst individuals with OA, who go on to have a stroke. Therefore, it is important for the clinical management of chronic stroke survivors with persistent gait asymmetries to know whether they are at risk of developing OA

and how to manage the interaction of the two conditions.

2.7 Study Aims and Objectives

Accordingly, the aim of this thesis s to characterise knee joint moments in a cohort of stroke survivors and to do so over time (assessed on two occasions: at baseline and at two-year follow-up). Where there is high asymmetry of knee joint moments between limbs and joint moments in otherwise healthy adults, there is greater risk of developing OA; therefore, to achieve our aim, the project's objectives are as follows:

1. To explore the difference in knee joint moments between stroke survivors' paretic and non-paretic sides.
2. To explore the difference in knee joint moments between paretic and non-paretic sides in severe and less severe spatiotemporal (swing time and step length) asymmetry sub-groups.
3. To explore the difference in knee joint moments between stroke survivors and healthy adults walking at both self-selected and slow speeds (matched to stroke survivors).
4. To explore the difference between paretic and non-paretic sides of severe and less severe asymmetry subgroups and healthy participants, with regard to their limbs while walking; with the healthy participants walking at self-selected and slow speeds (matched to the stroke survivors).
5. To explore the immediate effect of imposing symmetric gait pattern (based on a spatiotemporal symmetry) on knee joint moments in stroke survivors.
6. To determine individual changes in knee joint moments in a cohort of stroke survivors over 2-years.

Chapter 3: General Methods

3.1 Participants

After obtaining ethical approval from the University of Salford (HSCR14-106) and King Fahad Medical City (16-243) (see Appendices A.2 and B.2), a sample of adult (>18yrs) community-dwelling stroke survivors, both male and female, were recruited from previous studies and community support groups (for example, the Brain and Spinal Cord Injury Centre (BASIC)) in Greater Manchester, UK and King Fahad Medical City (KFMC), Saudi Arabia. A group of healthy adults (>18yrs), were recruited from the University of Salford's staff, previous studies at the University, and the CitizenScientist website to participate as a control comparison with the stroke participants' results.

The aim of this study was to characterise knee joint moment in the first instance. As this study is the first of its kind in the field, the recruitment criteria for the stroke participants was kept wide (all kinds of stroke survivor, so long as they had sufficient mobility to be able to take part safely in the protocol were included), in order to ensure high generalisability of the findings and to represent a wide stroke cohort. The inclusion and exclusion criteria for this study were set as follows:

- ***Inclusion Criteria:***
    - Stroke participants:

➢ Any individual diagnosed with first unilateral stroke (haemorrhagic or ischemic) at any time since onset.
➢ Ambulatory before stroke: pre-morbid modified Rankin Scale >3.
➢ Able to walk for more than 10 metres without physical assistance or a walking aid. Participants must have been able to complete 10m walk without assistance. Time to complete was NOT used as an inclusion/exclusion criteria (but was used to describe severity of impairments as per Section 3.3.1 below.
➢ No cognitive deficits and able to follow a three-step command (less than 24/30 in the mini-mental status exam).
➢ Medically stable, as indicated by discharge to community.

- Healthy participants:

- Healthy volunteers, self-reporting as free of any cardiovascular, musculoskeletal, or neurological injury or disease.

- ***Exclusion Criteria (for both the stroke and healthy participants):***

- Any pathology affecting walking ability (non-stroke-related disabilities).
- Inability to provide informed consent (due to receptive and/or expressive language problems).
- Any cardiovascular, musculoskeletal or balance deficits, or other disease/injury that could affect walking ability or cause unstable cardiac, medical and musculoskeletal conditions (for example, arthritis in the joints or a history of fracture), which would limit participation and alter gait pattern.

3.2 Sample Size

The sample size calculation was based on the first five participants and aimed to detect differences in the mean KAM impulse (reflected in the mean total medial knee load) amongst the asymmetric stroke survivors and healthy controls. Walking at matched- speed revealed a total sample size requirement of 17 per group (using a mean ±SD of 0.266 Nm/kg ± 0.079 for the healthy controls, 0.156 Nm/kg ± 0.088 for the stroke survivors, and an alpha of 0.05 with 95% power) (see Appendix A.5). However, while prospective power analysis (*priori power*) was conducted to determine the sample size, retrospective power analysis (*post hoc*) will obtained.

3.3 Procedures

3.3.1 Baseline Demographic Data for the Stroke Survivors

Clinical standardised and validated measures of functional recovery and motor control were taken to provide clinical descriptors of the stroke participants:

1. Ten-metre walk test

This is a common useful outcome measure, which helps to assess walking speed per second over a distance of 10 metres. It is considered to be a reliable and valid measurement for the post-stroke recovery stage (Perry et al., 1995), whereby speed is calculated by dividing the distance by time. The stroke survivors' self-selected walking speed was categorised as: speed

less than 0.4m/s (household ambulatory); 0.4-0.8 m/s (limited community), or speed greater than 0.8m/s (community ambulatory) (Perry et al., 1995).

2. Berg Balance Scale (BBS)

This is one of the functional balance outcome measures developed to assess balance in community-dwelling individuals. The Berg Balance Scale has been shown to have excellent reliability in assessing post-stroke survivors and elderly participants (Blum and Korner-Bitensky, 2008). It consists of 14 items, with a total score of 56. Each item is rated on a 5-point scale (0-4), with a higher score indicating better balance ability. Scores of 41-56 represent good balance (Blum & Korner-Bitenskyd, 2008).

3. Fugl-Meyer assessment of motor performance – lower extremity subscale

This is one of the most comprehensive quantitative measures for evaluating sensory and motor recovery after a stroke (Gladstone et al., 2002). Fugl-Meyer for the lower extremity includes different items that assess motor function, passive joint motion, and sensation. Each item is graded on a three-point scale (0=cannot perform, 1=performs partially, and 2=performs fully), with a maximum score of 34 and a higher score indicating better motor recovery.

4. Timed 'up and go' (TUG) test

The timed up and go (TUG) test is a clinical performance-based measure, used to evaluate lower limb mobility, function, and fall risk in different populations for various tasks (i.e. sit-to-stand, walking, turning, and stand-to-sit) (Ng and Hui-Chan, 2005). This test measures the time, in seconds that a participant takes to stand up from a chair, walk for three metres, turn, walk back to the same chair, and sit down. A time score of ≥14 s is specified as the high risk of fall threshold (Shumway-Cook et al. 2000; Andersson et al. 2006).

5. The Knee Osteoarthritis Outcome Score (KOOS)

This is a self-administered questionnaire that helps to evaluate knee-related issues. It contains 42 items in five separate subscales: symptoms and stiffness (7 items), pain (9 items), activities of daily life (17 items), functioning in sport and recreation activities (5 items), and knee-related quality of life (4 items) (Roos et al., 1998). Each item is scored from 0-100, with zero indicating extreme knee problems and 100 representing no knee problems. In this study, the KOOS pain

subscale was used, as it is considered to be a reliable and valid tool that is appropriate for use as a primary pain outcome measure of painful knee conditions (Roos et al., 1998; Roos and Toksvig-Larsen, 2003).

3.3.2 Three-dimensional Gait Analysis System Instruments

3D gait analysis data (kinematic) was recorded using 10 infrared cameras at a sampling frequency rate of 100 Hz (University of Salford site – Vicon Motion Systems, Oxford, UK; Saudi Arabia site – Qualisys AB, Gothenburg, Sweden), 3D gait analysis (kinematic) data were recorded. Meanwhile, kinetic data were obtained from embedded force plates sampled at 1000 Hz (University of Salford site – Kistler, Alton, UK; Saudi Arabia site – AMTI, Watertown, USA).

One of the most important steps in attaining the best possible accuracy in kinematic measurements is the calibration of the 3D system. Calibration enables the capture volume to be defined, thereby facilitating global reference, and the cameras to be appropriately positioned and orientated. The 3D coordination of the marker position is then created using data from each camera. Thus, dynamic calibration consists of moving through the capture volume and waving the wands (the Vicon system and Qualysis system wands) through as much capture volume as possible, enabling each camera to record the wand in several orientations. When calibration is complete, the calibration dialogue box in each system software will show the 'average residual' calibration result, which will give an assessment of the precision of the system user's calibration for each camera. The 'calibration residual' will indicate how well the data correspond to the calculations. The residual value should be less than 2.0, a lower number indicating a more effective calibration process.

Once the calibration process has been successfully completed, the next calibration step is performed by placing the wand frame (for Vicon/L-frame for Qualysis) in the capture volume, precisely at the corner of the first force platform, which represents the origin (0, 0, 0) of (X, Y, Z) axis, to the volume origin**.** This process allows the 3D system software to orient the cameras relative to the force platforms.

3.3.3 Marker Placement

Upon arrival at the University of Salford's gait laboratory and after completing the laboratory's process for preparing the data-collection procedure and signing the informed consent form, demographic data (age, weight and height) were collected. The participants subsequently changed into shorts and footwear that they had brought for the trial. Passive reflective markers were attached to the participants' limbs using a modified Calibrated Anatomical Systems Technique (CAST) modelling marker set (Cappozzo et al., 1995) (see Figure 3-1). Markers were then attached to the participants' skin, using hypo-allergenic double-sided tape over specific anatomical landmarks: bilaterally over the medial and lateral epicondyle of the distal femur; on the medial and lateral malleolus of the ankle; bilaterally on the heels; bilaterally over the head of the second metatarsal and the base of the first and fifth metatarsal; on the anterior superior iliac spine; on the posterior superior iliac spine; on the greater trochanter, and on the iliac crest.

Rigid plastic clusters of four markers were placed on the lumber spine at L3, the bilateral thighs, and the legs, secured with Fabrifoam SuperWrap bandages.

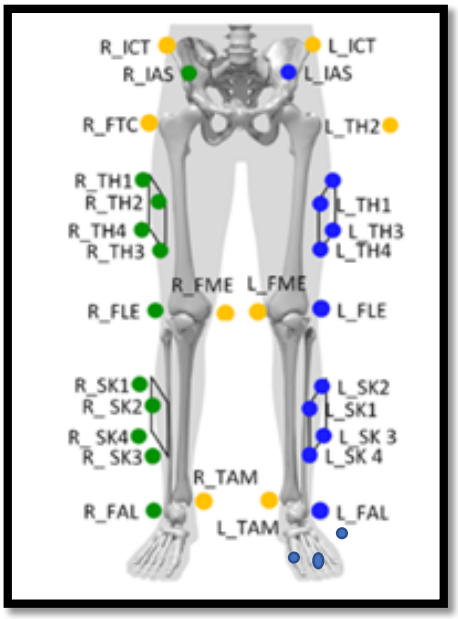


Figure 3-1: CAST model

3.4 Data Collection

Following the attachment of the markers, each participant was asked to stand in an 'T' position with arms outstretched for participant calibration (***static trial***), in order to adjust the

biomechanical model's parameters (i.e. segment lengths, orientations, and the position of the model's markers; see The data collected using the 3D motion analysis systems were recorded with Vicon Nexus (V.1.8.5) and Qualisys 2.3 Track Manager (QTMTM 2.3) software. Using this software, the markers in the recorded trials were labelled to define the body segments according to the proper anatomical landmarks (see Table 3-1). However, each trial was checked to verify the correct name of each marker and the proper segments, while at the same time deleting all unnecessary markers that appeared in the volume capture, due to noise or reflection. All dynamic trials were then saved (in C3D format) and exported to Visual3D software (C-Motion Inc, Germantown, USA). This created a biomechanical model based on the above marker set (see Figure 3-1).

Table 3-1 for the model segments). The participants were then asked to walk at least five times (***dynamic trials***) over a six-metre walkway (contact with the force platforms) at a comfortable speed. In addition to this comfortable speed, the healthy participants walked at two slower speeds (0.4 m/s and 0.8 m/s), coinciding with the threshold walking speeds suggested to reflect moderate and mild levels of impairment in community ambulation (Perry et al., 1995). However, comfortable walking speed was always performed first, followed by the two slower speeds in a randomised order. The slower walking speeds were controlled by monitoring and recording the time taken to walk the six metres, using a timing system gate (Brower Timing System, USA). The participants were also shown a digital clock, indicating how many seconds they had to reach the end of the walkway, if walking at the specified speed.

In addition to the above, the participants were given practice trials to familiarise them with the protocol and to become accustomed to walking at the prescribed speeds. Verbal instructions and feedback from the researchers accompanied this practice, such as: "Walk as you do normally" and "Keep your head straight and look ahead", in order to avoid changing the baseline gait pattern by having to adjust steps and target the force platforms. These trials were deemed to be successful for inclusion in the analysis, if the force platform captured at least one stance phase (i.e. the foot landing entirely on the force platform), and the walking speed for the slow walking trials fell within the average parameters.

3.5 Data processing

The data collected using the 3D motion analysis systems were recorded with Vicon Nexus (V.1.8.5) and Qualisys 2.3 Track Manager (QTM^{TM} 2.3) software. Using this software, the markers in the recorded trials were labelled to define the body segments according to the proper anatomical landmarks (see Table 3-1). However, each trial was checked to verify the correct name of each marker and the proper segments, while at the same time deleting all unnecessary markers that appeared in the volume capture, due to noise or reflection. All dynamic trials were then saved (in C3D format) and exported to Visual3D software (C-Motion Inc, Germantown, USA). This created a biomechanical model based on the above marker set (see Figure 3-1).

Table 3-1: Visual 3D model segments.

Segment	Proximal radius/joint	Distal radius/joint	Tracking markers
Pelvis	- Right anterior superior iliac spine - Left anterior superior iliac spine	- Right posterior superior iliac spine - Left posterior superior iliac spine	Pelvis cluster pad (4 tracking markers)
Thigh	- Hip joint centre• - Greater trochanter	- Medial femoral condyle - Lateral femoral condyle	Thigh cluster pad (4 tracking markers)
Shank	- Medial femoral condyle -Lateral femoral condyle	- Medial malleolus - Lateral malleolus	Shank cluster pad (4 tracking markers)
Foot	- Medial malleolus - Lateral malleolus	- 1st metatarsal head - 5th metatarsal head	Superior/inferior calcaneus, medial/lateral calcaneus
Virtual foot	-Medial malleolus floor - Lateral malleolus floor	- 1st metatarsal head floor - 5th metatarsal head floor	
•Hip joint centre is automatically calculated by using anterior and posterior superior iliac spine markers using the regression equation by Bell and Brand (1990)			

Five successful walking trials (from each session), with force plate data from one full stance phase on each limb for all the participants, were used in the analysis. Spatiotemporal, kinematic and kinetic data were processed using Visual3D. From body weight and height data, the biomechanical model helped to define segment masses and inertia to calculate joint kinematics and kinetics. Raw marker coordinates and kinetic data were smoothed using low-pass Butterworth digital filters to reduce the magnitude of noise by applying a cut-off frequency at 6 Hz and 25 Hz for the kinematic and kinetic data, respectively (Winter, 2009). Gaps in the kinematic trajectory due to missing frames of the measured data were filled through an interpolating process with a maximum of 10 frames. Walking events (for example, heel contact and toe-off) were detected by changes in the force platform data, thus determining the gait events for the left- and right-side gait cycles and stance phase information. Joint angles were computed through Cardan/Euler rotations X-Y-Z. In addition, a flexion/extension–adduction/abduction–internal/external rotation sequence was used, where flexion, adduction and internal rotations were derived as a positive angle. The mean and standard deviation values were then exported from visual 3D to Microsoft Excel 2017 (Microsoft, Washington, USA), from which each of the following outcome measures were obtained.

In order to estimate/calculate net knee joint moments, an inverse dynamic approach was used (Ren et al., 2008). This approach involved the acquisition of external force (GRF) data (using force plate systems) and 3D marker data (position, acceleration and velocity), which represented the biomechanical model and inertia properties of segments (mass, centre of mass, and moment inertia), using a motion capture system (for the moment calculation equation, see Figure 3-2). A combination of these data sets via an inverse dynamic process provided information about the net knee joint moment (peaks of external KAM and KFM and KAM impulse), thereby estimating knee load and reflecting the nature of the medial and anterior knee joint load (normalised to body weight) during walking (Creaby et al., 2013; Sharma et al., 1998). Joint moments were resolved in the proximal segment (for example, knee joint in reference to the thigh segment).

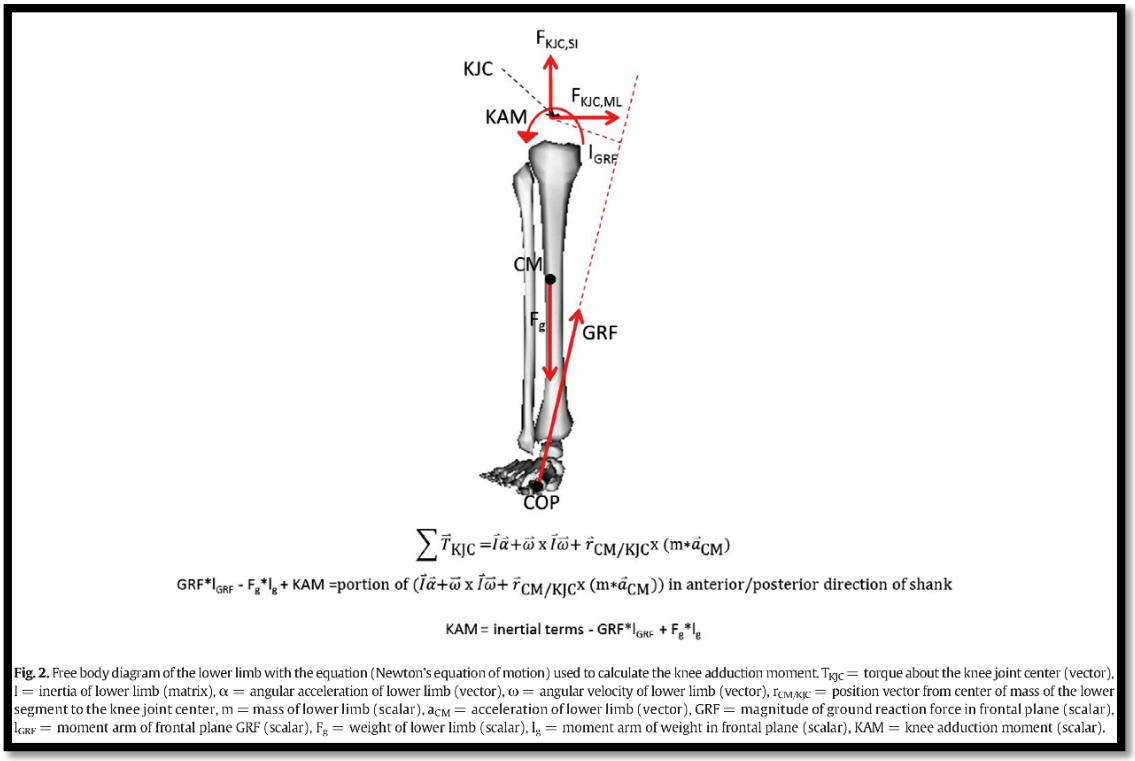


Fig. 2. Free body diagram of the lower limb with the equation (Newton's equation of motion) used to calculate the knee adduction moment. T_{KJC} = torque about the knee joint center (vector), I = inertia of lower limb (matrix), α = angular acceleration of lower limb (vector), ω = angular velocity of lower limb (vector), $r_{CM/KJC}$ = position vector from center of mass of the lower segment to the knee joint center, m = mass of lower limb (scalar), a_{CM} = acceleration of lower limb (vector), GRF = magnitude of ground reaction force in frontal plane (scalar), l_{GRF} = moment arm of frontal plane GRF (scalar), F_g = weight of lower limb (scalar), l_g = moment arm of weight in frontal plane (scalar), KAM = knee adduction moment (scalar).

Figure 3-2: Equation for the knee joint moment calculation equation (adapted from (Schmitz and Noehren, 2014)

Spatiotemporal gait symmetry was calculated as the ratio (maximum/minimum) of the values for each variable, including swing time and step length in the leg for each group (Patterson et al., 2010). Each participant was classified as asymmetric, when the normative cut-off ratio (upper 95% CI limit of symmetry in a healthy adult) of 1.06 for swing symmetry and/or 1.08 for step length symmetry, was exceeded (Patterson et al., 2010).

Compensatory gait patterns are common following a stroke (for example, hip hiking, knee joint RoM, and toe in/out) and are known to influence knee joint moments (Creaby et al., 2013; Dunphy et al., 2016; Farrokhi et al., 2015; Linley et al., 2010; Shull et al., 2013). These compensatory mechanisms are correlated with external knee joint moments involving the knee (Chiba et al., 2016), because measuring the knee joint moment is principally determined by the product of GRF and moment arm to estimate external adduction loads. The manipulation of these two components is arguably the main biomechanical factor measured by motion analysis systems and they have received maximum attention in recent years, mainly in relation to their proposed association with altered joint moments and knee osteoarthritis (OA) (Simic et al., 2011; Simic et al., 2013; Telfer et al., 2017). Accordingly, such

compensatory patterns were measured here to provide a context against which to interpret observed joint moments. Meanwhile, hip hiking was measured as the magnitude of coronal plane pelvic obliquity at the time of maximum peak KAM on the contralateral side (i.e. the stance limb), while the toe-out angle was defined as the maximum external rotation of the foot with respect to the direction of forward progression. Moreover, knee joint angle was calculated as the maximum knee flexion angle of stance.

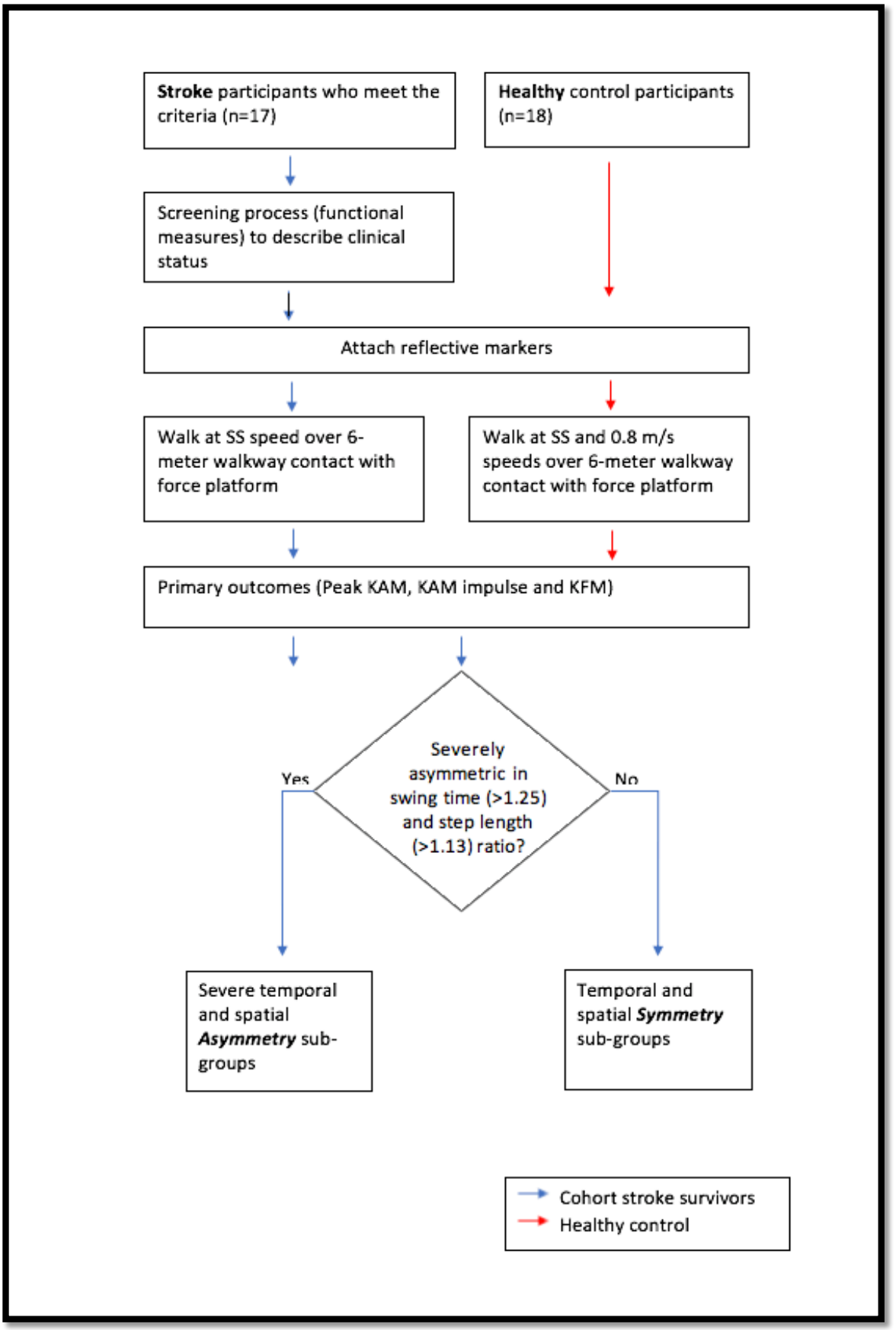


Figure 3-3: Study procedure flow chart.

3.6 Main Outcome Measures

- **Primary outcomes:**
  - 1st peak (first 50% of stance) external KAM.
  - KAM Impulse.
  - Overall peak external KFM.
- **Secondary outcome:**
  - Kinetic data: Maximum external joint moments of the hip, knee, ankle and GRF.
  - Kinematic data: Maximum joint angles of the pelvis, hip, knee and ankle.
  - Temporal and spatial parameters (walking velocity, step length, stance time and swing time).

3.7 Statistical Analysis

In this thesis, a number of studies have been reported, which require different statistical approaches. These have been summarised here for each of the research questions addressed.

Descriptive measures (mean ± standard deviation (SD) and 95% confidence intervals (CI)) of the participants' characteristics were used to gather details of all the study samples across the different groups. All dependent variables were tested for normality using Shapiro-Wilk tests. If a test was insignificant ($p>.05$), it indicated that the distribution did not differ significantly from normal distribution. Dependent variables that violated the assumption of normality were rank-transformed prior to further analysis.

Main Study

There were *a priori* hypotheses that the knee joint moment metrics would differ between:

1) Paretic and non-paretic limbs in the group of stroke survivors.
2) Paretic and healthy participants' limbs and non-paretic and healthy participants' limbs while walking, when healthy participants walked at self-selected and slow speeds (matched to the stroke survivors).
3) Paretic and non-paretic sides within severe and less severe spatiotemporal (swing time and step length) asymmetry subgroups.

4) Paretic and non-paretic sides in severe and less severe asymmetry subgroups and healthy participants' limbs while walking, when the healthy participants walked at self-selected and slow speeds (matched to the stroke survivors).

Accordingly, each of these hypotheses (1-2) were tested individually, using analysis of (co)variance (ANOVA/ANCOVA). However, descriptive statistics were used to test the other hypotheses (3-4) for the subgroups of stroke survivors with temporal and spatial asymmetry.

Effect sizes (ES) and the corresponding CI, using the Cohen's *d* method (Cohen, 1992), were calculated (using G*Power Version 3.1.1, Universität Kiel, Germany) for the following comparisons, in order to examine the extent of the difference between groups/subgroups. ES were interpreted as: trivial effect=d <0.2, small effect=d <0.5, medium effect=d 0.8, and large effect=d ≥0.8). The corresponding 95% CI of ES was also provided by using the following formula (Lee, 2016):

$$\sigma(d) = \sqrt{\frac{N_1+N_2}{N_1 \times N_2} + \frac{d^2}{2(N_1+N_2)}}$$

$$95\%\ \text{CI for Cohen's } d\text{: } [d - 1.96 \times \sigma(d),\ d + 1.96 \times \sigma(d)]$$

(N: The sample size of group 1 and 2)

For hypotheses 1-2, five strides of KAM impulse, peak KAM, and peak KFM were calculated for each participant and compared between the groups at the self-selected walking speed, using one-way (between-group) ANCOVA (one comparison for the paretic limb vs. healthy limb, and another comparison for the non-paretic limb vs. healthy limb), with walking speed as the covariate. These same measures were also compared amongst the stroke survivors walking at SS speed and the healthy participants walking at 0.8 m/s in one-way (between-group) ANOVA (one comparison for the paretic limb vs. healthy limb, another comparison for the non-paretic limb vs. healthy limb). Repeated-measure ANOVA was then used to test the differences between limbs amongst the stroke survivors (paretic vs. non-paretic) for each of

the outcome measures. In addition, a two-way repeated-measure ANOVA was used to compare joint moments between visits (one and two) and between limbs (paretic vs non-paretic) in the stroke survivors. Bonferroni corrections for repeated testing were applied and the level of significance was set as $P<0.05$. All tests were performed using SPSS V. 24.0 (SPSS Inc., Armonk, USA).

For hypotheses 3-4, according to the normative mean values of swing time and step length asymmetry ratios reported for the stroke survivors (median 1.25 and 1.13, respectively, measured in 161 stroke survivors) (Patterson et al 2010), the participants were classified into two groups based on their swing time asymmetry (severe temporal asymmetry ratio [asymmetric] >1.25, mild-moderate temporal asymmetry ratio <1.25 [symmetric]), asymmetry of step length (severe spatial asymmetry ratio [asymmetric] >1.13, and mild-moderate spatial asymmetry ratio <1.13 [symmetric]). Swing time and step length symmetry ratios were calculated as the ratio between the two legs (maximum/minimum).

One of the purposes of this PhD work was to discern the difference between paretic and non-paretic sides in joint moments within severe and less severe spatiotemporal (swing time and step length) asymmetry subgroups. Accordingly, the cohort group of stroke survivors (n=17) was split into small and unequal subgroups based on the reported swing time and step length ratios (Patterson et al., 2010). Consequently, this was to limit statistical power, and a full statistical analysis is inappropriate for detecting changes between subgroups (Chen et al., 2005; Weissgerber et al., 2015). Therefore, a comparison of the mean of each subgroup with 95% CI relating to the mean values of the healthy controls, walking at different speeds, was used to determine whether the joint moments were 'significantly different' from those of the healthy control group. Specifically, joint loads were considered 'high', if the mean exceeded the 95% CI upper limit demonstrated by the healthy participants; 'low', if the mean fell below the 95% CI lower limit, and 'comparable', if the mean was within the lower and upper limit of 95% CI in the healthy participants. However, ES for the differences between subgroups was characterized using *d* (Cohen's $d > 0.80$).

3.8 Test-Retest Repeatability of Lower Limb Time-Distance, Kinetic and Kinematic Gait Parameters

3.8.1 Introduction

Motion-analysis System Reliability and Marker Placement

Analysing human movement requires the collection of mechanical data for the musculo-skeletal system while a motor task is being performed; for example, using 3-D movement analysis, or any of the many other systems in general use today for measuring body displacement over a period of time (Cappozzo et al., 2005). However, measurements and measurement instruments should be reliable, valid, and responsive to any clinical change that may occur over time (Medved, 2000). Reliability describes how uniformly a test can be reported when carried out on several different occasions, using different measuring tools.

With any motion-analysis system that requires the attachment of skin reference markers to anatomical landmarks, it is vital for marker placement to correspond closely to the relevant underlying skeletal segments and to be done in a way that reduces the effect of skin movement to a minimum. Skin movement artefacts, i.e. the relative movement between the marker base and underlying bone, are mainly associated with the interposition of soft tissues, and will vary in different regions of the body (Kuo et al., 2008). However, there is often cause for concern over the degree of skin movement observed in such studies. The proportion of error that this causes in the final results will depend on the parameters being measured. For example, marker movement has little effect on the knee angle on the sagittal plane, as this causes relatively little change over longer segments. However, it may cause substantial errors in transverse-plane measurements, or in measurements involving shorter segments, such as in the foot (Whittle, 2007). The possible sources of error will include the type, size and the location of the markers; the effects of age, body structure, growth and stress on gait data; system errors; artefact and calibration errors, and assessor bias, resulting from inaccuracy or a lack of training. Meanwhile, the reliability of the measurements will depend on various key factors, such as the daily calibration of the cameras, the accuracy of marker placement, good and effective training of the team, and system updates (McGinley et al., 2009; Yavuzer, 2009).

For the purpose of eliminating sources of measurement error, Cappozzo et al. (1995) suggest the CAST (Calibrated Anatomical System Technique) Protocol, aimed at minimising soft-tissue artefacts. In this Protocol, markers are not positioned on anatomical landmarks; rather, clusters of around four markers are attached to the feet, legs, thighs and pelvis. The positions of these anatomical landmarks are then fixed according to where the cluster is located in the corresponding body segment. Most importantly, the CAST marker set uses six degrees-of-freedom (DOF) to track the segments, allowing more rotation and translation at each joint than can be achieved with other marker sets, such as the Helen Hayes, which uses three DOF (Collins et al., 2009). According to a recent repeatability study by Ppinzone et al. (2015), the CAST model is suitable for clinical gait analysis, with results of the above study indicating that the CAST model has an acceptable frequency of clinical measurement error for lower limb kinematic variables (SEM <3.9°, except in hip rotation, which exceeded 5°), based on (McGinley et al., 2009) recommendations.

3.8.2 Study Aim

The aim of this study was to examine the repeatability (between two visits) of the investigators' marker placements on the lower limbs of healthy participants, on different planes and according to kinematic, kinetic and GRF data, and spatiotemporal parameters.

3.8.3 Methods

Healthy young adults attended the lab on two separate occasions and underwent the same testing procedures as described in the Methods Chapter (see section 3.3), in order to achieve the first objective, with regard to establishing the test-retest repeatability of spatiotemporal, kinetic and kinematic data collection procedures. The reasons for recruiting a young healthy sample (rather than stroke survivors, or older adults) related to the challenge of conducting reliability studies on stroke survivors with adequate numbers of participants being retained, because of the number of visits and the short interval time between visits (2-7 days). Another reason was that it was unclear whether the nature of the pathological gait pattern would have any direct effect on procedural sources of error, such as marker placement (McGinley et al., 2009).

According to (McGinley et al., 2009) systematic review, the sampling method for recruiting gait participants in reliability studies is rarely reported. While there is no consensus as to the number of subjects required to obtain adequate stability for reliability measures, the above-mentioned review paper (23 studies) showed that the median sample size of the papers that were included amounted to n=10 participants. However, the sample size of the studies in this review was not justified in every case. Meanwhile, factors such as walking speed and footwear were controlled across the measurements (Robbins and Maly, 2009; Shakoor et al., 2010).

3.8.3.1 Statistical Analysis

It is important to ensure that the investigator undertakes reliable marker placement to examine the between-days repeatability (test-retest) of kinematic, kinetic and spatiotemporal data. In order to achieve this, intraclass correlation coefficients (ICCs), the coefficient of multiple correlations (CMC), and the standard error of measurement (SEM) (within the participants' standard deviation) were used in this study.

The CMC was used, as recommended by Kadaba et al. (1989), to examine the similarity and consistency between two representative waveform parameters (i.e. kinematic and kinetic) within a specific range. The CMC is a dimensionless measure, which combines mean behaviour and observed variation in the data across a gait cycle (Røislien et al., 2012). Accordingly, the CMC is calculated as a ratio of the variance in the mean to the total variability of the grand mean at a specific point in time and in several between-test trial sessions (five trials for each session). The CMC values in this study were interpreted as follows: 0.95–1: excellent; 0.85–0.95: very good; 0.75–0.85: good; and 0.65–0.75: moderate.

The second measure of reliability consisted of ICCs (ICC (3,1) is here used as a measure of between repeated measurements (Weir, 2005)) and their 95% confidence intervals, which were used for the spatiotemporal variables (CMC was not used, because it is not applicable to spatiotemporal variables, but is rather a value that is connected to kinematic and kinetic data). In this sense, ICC values of 0.75 or higher were considered to be excellent, 0.40–0.74 to be fair to good, and 0.40 or lower to be poor (Rankin and Stokes, 1998).

Evaluation using ICCs and CMC provides information on the relative reliability of measurements, but it can be of limited help when determining whether an observed change is due to changes in actual performance. Therefore, SEM was applied (as recommended by Bland and Altman (1996)) to quantify the variability in spatiotemporal (walking speed, step length, swing time and stance time), kinematic (joint angles), and kinetic (moment and GRF) measurements between sessions. This absolute measure (SEM) provided information on the magnitude of typical errors in the specific measurement being examined. It was measured in the units of interest (the degree of joint ROM and Nm/kg for the joint moment) and in percentages of the grand mean (%SEM).

3.8.4 Results

3.8.4.1 Participants

Eight healthy adult participants from the University of Salford were recruited to participate in this study. Demographic data is presented in Table 3-2.

Table 3-2: Demographic data

Participants Characteristics		
Gender	*Male (N=7)*	*Female (N= 1)*
Age (year)	34.9 (4.7)	
Height (M)	1.7 (0.07)	
Mass (kg)	69 (7.8)	
Walking speed (m/s)	1.29 (0.35)	

3.8.4.2 Spatiotemporal, kinematic, and kinetic variables

The results of the spatiotemporal parameters showed 'excellent' repeatability for walking speed, step length, stance, and swing time parameters (ICC>0.87), with low SEM <0.06° (see Table 3-3). In fact, the overall results of the kinematic variables showed 'good-excellent' repeatability, with an average CMC of between 0.74 to 0.99, and with a SEM < 2.4° (see Table 3-4). Very high repeatability (CMC>0.90) was found for pelvic obliquity, pelvic rotation, all hip angles, knee flexion and ankle dorsiflexion/plantarflexion. For the majority of the variables, SEM was less than 2°, except for knee flexion, knee rotation and ankle adduction/abduction.

For the kinetic variables, the overall results demonstrated 'very good-excellent' repeatability of joint moments and GRF (CMC >0.93), except for the ankle joint moment on the frontal plane, which showed 'good' repeatability (CMC=0.75) (see Table 3-5).

Table 3-3: Intraclass correlation coefficients (ICC), 95% confidence intervals (CI), standard error of measurement (SEM) and %SEM ((SEM/Mean) *100)) of spatiotemporal variables.

Spatiotemporal	Mean (SD)	ICC	95% CI	SEM	% SEM
Walking speed (m/s)	1.29 (0.35)	0.97	0.85-0.99	0.06 (m/s)	4.7
Step Length (m)	0.70 (0.05)	0.98	0.90-1.0	0.02 (m)	2.9
Stance Time (s)	0.69 (0.07)	0.89	0.44-0.98	0.02 (s)	4.34
Swing Time (s)	0.44 (0.03)	0.87	0.34-0.98	0.01 (s)	2.27

Table 3-4: Mean and SD of the coefficient of multiple correlations (CMC), standard error of measurement (SEM) and %SEM ((SEM/Mean) *100)) of pelvic, hip, knee and ankle kinematic variables on the sagittal and frontal planes.

Joint angle	Plane	Mean (SD) (°)	CMC	SD	SEM (°)	%SEM
Pelvic Angles (°)	x	2.99 (0.76)	0.74	0.17	0.58	19.56
	y	4.32 (0.48)	0.95	0.02	0.56	12.90
Hip Angles (°)	x	24.96 (1.26)	0.99	0.01	1.82	7.29
	y	7.76 (0.77)	0.97	0.02	1.02	13.18
Knee Angles (°)	x	64.45 (1.37)	0.99	0.00	2.22	3.43
	y	5.93 (0.97)	0.82	0.16	1.33	22.45
Virtual Angles (°)	x	18.02(0.90)	0.96	0.02	1.55	8.62
	y	8.20(2.19)	0.79	0.12	2.39	29.12

Table 3-5: Mean and SD of the coefficient of multiple correlations (CMC), standard error of measurement (SEM) and %SEM ((SEM/Mean) *100)) of pelvic, hip, knee, and ankle kinetic variables on the sagittal and frontal planes

Joint Moment	Plane	Mean(SD) (Nm/kg)	CMC	SD	SEM (Nm/kg)	%SEM
Hip Moments (Nm/kg)	x	0.74 (0.09)	0.97	0.01	0.06	8.60
	y	0.97 (0.05)	0.98	0.01	0.05	5.43
Knee Moments (Nm/kg)	x	0.48 (0.04)	0.93	0.06	0.04	8.66
	y	0.56 (0.04)	0.98	0.01	0.02	3.77
Ankle Moments (Nm/kg)	x	1.35 (0.04)	0.98	0.01	0.06	4.18
	y	0.14 (0.02)	0.75	0.23	0.03	20.21
GRF (N/Kg)	x	0.06 (0.01)	0.94	0.04	0.01	10.58
	y	0.18 (0.01)	0.98	0.00	0.01	7.35
	z	1.01 (0.02)	0.94	0.04	0.08	8.05

3.8.5 Discussion

The aim of this study was to determine the repeatability (between two visits) of the investigators' marker placements on the lower limbs of healthy participants, in order to determine kinematic and kinetic data alongside GRF data and spatiotemporal parameters. The findings of this study confirm that the placement of the markers at the different visits and for the kinematic and kinetic parameters was repeatable. This was further confirmed with a repeatable assessment of the spatiotemporal parameters, calculated from the 3D collection.

The ICC result of the spatiotemporal parameters (walking speed, step length, stance time and swing time) showed 'excellent' repeatability (>0.87). The results of the current study were therefore consistent with those obtained from a recent study by (Meldrum et al., 2014), which demonstrated high repeatability of spatiotemporal ICC<0.90, with low SEM (less than 5% measurement error).

The results of the CMC values for the kinematic parameters of the sagittal and frontal planes showed high repeatability (>0.74: moderate-excellent). Moreover, the sagittal plane variables displayed 'excellent' repeatability (>0.96), except for pelvic tilt, which showed only 'moderate' repeatability (CMC=0.74). The sagittal plane results corresponded to those of previous studies (Kadaba et al., 1989; Tsushima et al., 2003); reporting high repeatability of

all motion angles, except for pelvic tilt. According to Kadaba et al. (1989), the low value of CMC in pelvic tilt is due to the CMC calculation, which could be attributed to a small range of motion. In addition, according to (Della Croce et al., 2005), a minor degree of misplacement of markers on the anterior superior iliac spine (ASIS) and posterior superior iliac spine (PSIS) is one source of error that reduces reliability. However, there is a higher CMC value of pelvic tilt in this study compared to previous studies (Kadaba et al., 1989; Tsushima et al., 2003), which is potentially be due to a different pelvis model system being used, such as a different number of markers.

On the frontal plane, the current study's results showed higher repeatability (CMC 0.79-0.95) than those of Kadaba et al. (1989), while being consistent with those of Tsushima et al. (2003). This difference in results between studies may be due to the different biomechanical model used, which helped to reduce measurement variations/errors (pinzone et al., 2015).

Based on a recommendation of McGinley et al. (2009), the SEM for most of the joint motion in the current study showed highly acceptable measurement variation/error between visits (SEM<2°), except in knee flexion and ankle adduction/abduction (SEM 2.22°, and 2.39° respectively), where there was reasonable error.

The overall results of the CMCs in this study, with regard to the lower limb kinetic variables (joint moments and GRF) showed high repeatability (>0.93: very good-excellent), except for the ankle joint moment on the frontal plane, which showed less repeatability (CMC=0.75). These results are in agreement with previous studies by Kadaba et al. (1989) and Growney et al. (1997). The decrease in the CMC ankle joint value on the frontal plane in previous studies is suggested as being due to the small moment arm to the ankle joint centre (as a distal joint), which increases the sensitivity of the frontal plane moment calculation (Kadaba et al., 1989).

The SEM for the joint moments in this current study demonstrated lower incidence of measurement error on the sagittal and frontal planes, compared to the moment values of the hip, knee and ankle joints (%SEM $\leq$8.66%). However, while the SEM of ankle joint moments on the frontal plane was very low, the measurement error was considered to be 20% of the total ankle joint moment value. This higher percentage of error in the frontal plane ankle joint

moment may have been due to the small moment arm to the center of the ankle joint (Kadaba et al., 1989).

The most useful measurement for assessing changes to individuals' outcomes in a research study and clinical setup is fundamentally related to the degree of measurement error. This is very important for ensuring confidence that the difference between measurements is true (McGinley et al., 2009); signifying high reliability and a low degree of measurement error in this current study (especially for KAM and KFM %SEM $\leq$8.66%), as well as enhancing confidence for future studies, as the results have greater accuracy and are not merely the consequence of measurement variability. All percentage differences for knee joint moments of KFM and KAM variables exceed the %SEM values of 8.7% and 3.7%, respectively; indicating real joint moment measurement changes between sessions.

3.8.6 Limitations

One of the main limitations of this reliability study was the recruitment of a healthy sample of young adults (mean age of 35 years), walking at SS walking speed, which limits generalisability to older subjects and stroke survivors. However, these study participants were specifically selected to ensure a standardised study design, which excluded additional sources of variability; for example, gait pathology, high BMI, and different walking speeds and ages. This was important, since the current study's methods depended solely on the repeatability of the investigators' marker placements (Taylor et al., 2010), which is the main source of measurement error.

Given that a stroke population are included in this thesis (see subsequent chapters), previous studies have reported a high test-retest repeatability for spatiotemporal and kinematic variables in subjects with gait pathologies, such as due to stroke (Yavuzer et al., 2008). It is unlikely that pathological gait pattern has any direct effect on procedural sources of error, like marker placement ((McGinley et al., 2009), therefore the main source of measurement error (marker placement) in gait measures among this healthy cohort is likely to be generalisable to any adult patient group. However, the influences of pathological gait patterns on kinetic measures and the stability of these in patient groups, like stroke survivors requires further investigation. Importantly, although gait mechanics are known to change

with age (Levine et al., 2012), Rudolph et al. (2007) found no significant differences in SS walking speeds or knee joint moments (KFM and KAM) in groups of young, healthy (mean 20.6: 18-25 years), middle-aged (mean 49.2: 40-57 years) and older (mean 68.8: 60-80 years) subjects.

3.8.7 Conclusion

In conclusion, this test-retest repeatability study of investigators' marker placements on the lower limbs of healthy participants estimates the minimal difference in gait kinematics and kinetic parameters that can be attributed to measurement error. This margin of error was found to fall within that of previous studies, thus promoting confidence that the investigator can repeatedly collect biomechanical data from individuals, with minimal error in future studies.

Chapter 4: Does Knee Joint Loading in Long-Term Stroke Recovery Indicate a Risk of Joint Degeneration?

This chapter investigates knee joint loading in long-term stroke survivors and the potential risk of joint degeneration as a result. It sets out to achieve this by exploring the differences between sides in external knee joint moment amongst stroke survivors, based on the severity of the spatiotemporal asymmetry, compared to healthy controls walking at SS and slow walking speeds.

4.1 Background

Knee joint OA risk factors reveal OA to be a multifactorial disease, driven by mechanical factors in the context of systemic susceptibility (Andriacchi et al., 2015). Stroke is a condition that mainly affects individuals suffering from obesity, or else develops with increasing age. Therefore, these risk factors overlap the risk of developing OA; leaving subjects with lasting gait asymmetry (Zhang & Jordan, 2010). However, despite the plethora of possible stroke-related biomechanical contributors to the development of knee OA, very few studies have investigated whether gait impairments following stroke alter KAM and KFM in a way that would indicate the risk of joint degeneration (based on a systematic literature search; see Appendix A.7). As a result of previously noted variability between stroke survivors (Marrocco et al., 2016), it remains unclear whether gait impairments following stroke alter joint moments in such a way as to increase the risk of comorbid knee joint OA.

Clinically, a definitive understanding of knee loading patterns following stroke, and of whether these represent a known risk of developing OA, is important to help clinicians prioritise gait rehabilitation goals. In turn, this will limit the potential risk of joint degeneration, while also promoting an increase in physical activity. Therefore, the aim of this study was to characterise knee joint moments in a cohort of stroke survivors, comparing the paretic and non-paretic sides, divided into severe and less severe ***spatiotemporal*** (swing time and step length) ***asymmetry*** sub-groups. Both asymmetrical knee joint moments between limbs, and joint moments that exceed the recommended measurements indicate a risk of developing OA.

4.2 Methods

The methods applied in this study are similar to those outlined in the general Methodology Chapter (see Chapter 3, section 3.3). The data were collected at two sites: the University of Salford (Manchester, UK) and the Rehabilitation Hospital (Riyadh, Saudi Arabia). Meanwhile, stroke survivors were recruited from community support groups in Greater Manchester and at King Fahad Medical City (KFMC), Saudi Arabia. The stroke survivors' inclusion and exclusion criteria for this study were established as described in section 3.1. Also participating were a group of healthy adults (>18 years old), recruited from previous studies at the UK site. At each site, the present study received approval from the institutions' ethics committees, and all the participants were provided with written informed consent prior to participation.

Demographic data (age, weight and height), as well as clinically standardised, validated measures of functional recovery and motor control were documented. The following measures were used: walking speed over a six metre walking path; the Berg Balance Scale; the Fugl-Meyer Assessment of Motor Performance (lower extremity subscale); the Timed Up and Go test, and the Knee Osteoarthritis Outcome Score. The participants were subsequently fitted with passive single-reflective and cluster markers, using the CAST marker. These markers were attached to the participants' skin with hypo-allergenic tape over specific anatomical landmarks: the medial and lateral malleolus of the ankle; the anterior superior iliac spine; the posterior superior iliac spine; the greater trochanter, and the iliac crest, as well as bilaterally, over the medial and lateral epicondyle of the distal femur; the heels; the head of the second metatarsal, and the base of the first and fifth metatarsals. Meanwhile, rigid plastic clusters of four markers were placed on the lumber spine at L3, the bilateral thighs, and the legs, secured with Fabrifoam SuperWrap bandages.

The participants walked along a six-metre walking path for a minimum of five trials. Kinetic data were obtained from embedded force plates, and kinematic data were collected using a motion capture system. Because loading at the knee is influenced by gait speed (Robbins & Maly, 2009), the healthy participants walked at their self-selected (SS) pace, as well as at a slower speed (0.8 m/s), which corresponded to the mean walking speed of the stroke survivors. Walking speed was controlled by recording the time taken to complete the six-

metre walking path, using timing gates (Brower Timing Systems, Draper, UT, USA) at the start and end of the walkway. The stroke survivors walked only at their SS pace.

A minimum of five walking trials were used for analysis, using force plate data for one full stance phase on each limb from all the participants. Spatiotemporal, kinematic and kinetic data were processed with Visual3D (C-Motion, Inc., Germantown, MA, USA). Raw marker coordinates and kinetic data were filtered with a Butterworth filter at low-pass cut-off frequencies of 6 Hz and 25 Hz, respectively.

Using the inverse dynamics approach, the means of each participant's peak external KAM (first 50% of stance), KFM (overall peak), and KAM impulse were calculated as estimates of medial and anterior knee joint load during walking. All measures were then normalised to body weight. Spatiotemporal gait symmetry was calculated as the ratio (maximum/minimum) of swing time and step length between legs. Because compensatory gait patterns, which are common following stroke (for example, hip hiking, knee joint range of motion [RoM], and toe in/out), are known to influence knee joint moment, these were measured to provide a context for interpreting observed joint moments. Hip hiking was measured as the magnitude of pelvic obliquity on the coronal plane, at the time of maximum peak KAM on the contralateral side (stance limb). Meanwhile, the toe-out angle was defined as the maximum external rotation of the foot, with respect to the direction of the forward progression. Finally, knee joint angle was calculated as the maximum knee flexion angle during stance.

4.2.1 Statistical Analysis

All dependent variables were tested for normality using the Shapiro-Wilk test. Dependent variables that violated the assumption of normality were rank-transformed, prior to further analysis. Knee loading measures (peak KAM, KAM impulse and peak KFM) were compared between groups at SS walking speeds, using one-way ANCOVA, with walking speed as the covariate. These same measures were also compared between stroke survivors walking at SS speeds, and healthy participants walking at 0.8 m/s in one-way ANOVA.

One of the purposes of this PhD work was to distinguish between joint moments on the paretic and non-paretic sides in severe and less severe ***spatiotemporal*** (swing time and step length) ***asymmetry*** sub-groups. Accordingly, the cohort of stroke survivors (n=17) was split

unevenly into small sub-groups, based on their reported swing time and step length ratios (Patterson et al., 2010). Consequently, the statistical power of the present study is limited, with full statistical analysis being inappropriate for detecting changes between the sub-groups (Chen et al., 2005; Weissgerber et al., 2015). Therefore, the mean of each sub-group was used to determine whether the joint moments were 'significantly different' from those of the healthy control group, with 95% CI relating to the mean values of the healthy controls walking at different speeds. ES, using Cohen's *d* method (Cohen, 1992), were calculated with G*Power Version 3.1.1 (Universitat Kiel, Germany).

4.3 Results

4.3.1 Post-hoc Power Analysis

A post-hoc power analysis calculation demonstrated that for an alpha value of 0.05, the power was 0.67, showing the sample size to be inadequate for obtaining significant results. For instance, to achieve 80% power, the necessary sample is around 28 for healthy subjects and 30 for stroke survivors (see Appendices A.8.1 and A.8.2).

4.3.2 Participants

Stroke cohort

A total of 17 stroke survivors (Salford n=15, Saudi n=2) participated in this study. The mean (SD) walking speeds of all participants are summarised in Table 4-1.The mean walking speed of the stroke survivors reflects moderate and mild levels of impairment in community ambulation (Perry et al., 1995). According to the suggested cut-off ratio of the healthy population's swing time symmetry (1.06), 14 stroke survivors (82.4%) were found to be asymmetric. In contrast, eight stroke survivors (47.1%) displayed step length asymmetry (six with a longer paretic side), based on the cut-off ratio for the healthy population's step length symmetry (1.08) (K. K. Patterson et al., 2008).

The participants' characteristics, according to the asymmetrical sub-groups, are summarised in Table 4-1. All the stroke survivors demonstrated a prolonged swing time on the paretic side and prolonged stance time on the non-paretic side. However, the direction of the step length asymmetry varied between the participants and the temporally and spatially asymmetrical

stroke survivors; 60% of the ***temporal asymmetry*** sub-group, 71.4% of the ***temporal symmetry*** sub-group, 100% of the ***spatial asymmetry*** sub-group, and 54.5% of the ***spatial symmetry*** sub-group displayed a longer step length with the paretic limb. Moreover, the stroke survivors with asymmetry had more recently experienced the onset of stroke and walked more slowly than those without asymmetry. Finally, in all sub-groups of stroke survivors, pelvic obliquity was more pronounced than in the healthy controls. However, the ***temporal asymmetry*** and ***spatial symmetry*** sub-groups showed a remarkable increase in pelvic obliquity, compared to the other sub-groups.

Healthy control cohort

The clinical and demographic descriptors of all the participants are summarised in Table 4-1. No significant differences were found between the left and right legs for any measure of KAM or KFM (see Appendix A.4). The mean of both legs was therefore used in statistical comparisons between stroke survivors.

Table 4-1: Participant demographics – continuous variables are presented as means (SD), while nominal variables are presented as numbers. Mean values for gait parameters are provided for SS and 0.8 m/s walking speeds in the healthy control participants. Swing time and step length symmetry ratios are calculated as the ratio between the two legs (maximum/minimum). Positive values of pelvic obliquity indicate frontal hike of the ASIS marker on the swing side.

Groups	Stroke survivors					Healthy Control	
	Whole group	Sub-groups					
		Temporal		Spatial		SS	0.8 m/s
		Asymmetric >1.25	Symmetric <1.25	Asymmetric >1.13	Symmetric <1.13		
N	17	10	7	6	11	18	
Age (years)	64.0 (13.1)	64.0(12.7)	61.4(14.7)	59.2(11.2)	65.1(14.1)	44.6(15.4)	
Sex							
Male	14	8	6	5	9	15	
Mass (Kg)	75.9(11.1)	73.4(12.8)	79.6(7.8)	69.2(9.6)	79.6(10.5)	73.1(9.7)	
Height (m)	1.7(0.1)	1.7(0.1)	1.7(0.1)	1.7(0.1)	1.7(0.1)	1.7(0.1)	
BMI (Kg/m²)	25.9(3.8)	25.7(4.5)	26.3(2.9)	23.2(1.5)	27.5(3.9)	24.9(2.7)	
TUG (seconds)	14.5 (5.0)	16.4(5.7)	11.9(2.3)	14.3(5.4)	14.7(5.1)	n/a	
Time since stroke (years)	5.8 (10.8)	3.1(1.9)	9.7(16.7)	3.0(2.3)	7.4(13.4)	n/a	
BBS	50.7(5.2)	49.6(6.3)	52.3(2.8)	51.0(5.3)	50.6(5.4)	n/a	
Fugl-Meyer lower limb	25.7(4.6)	24.9(5.0)	26.9(3.9)	26.0(4.4)	25.6(4.8)	n/a	
KOOS Pain subscale	98.5(3.0)	98.9(2.7)	98.0(3.5)	99.5(1.1)	97.9(3.5)	n/a	
Affected side							
Left side	9	5	4	2	7	n/a	
Right side	8	5	3	4	4	n/a	
Walking speed (SS) (m/s)	0.8(0.2)	0.73(0.2)	0.93(0.25)	0.75(0.2)	0.85(0.3)	1.42(0.23)	0.87 (0.19)
Swing time symmetry (ratio)	1.3(0.24)	1.44(0.2)	1.09(0.07)	1.3(0.1)	1.3(0.3)	1.03 (0.02)	1.03(0.03)
Step length symmetry (ratio)	1.1(0.20)	1.16(0.13)	1.06 (0.08)	1.26(0.1)	1.05(0.04)	1.03 (0.02)	1.05(0.06)
Pelvic obliquity angle (at time of peak KAM) (°)						-3.71(2.51)	-2.662(2.80)
Paretic	1.0(3.1)	1.8(3.0)	-0.08(3.0)	0.6(2.9)	1.26(3.3)		
Non-Paretic	-1.8(2.7)	-2.6 (1.7)	-0.7(3.6)	-1.2(2.8)	-1.8(2.8)		
Knee flexion angle (°)						45.54(5.67)	45.00(6.52)
Paretic	36.4(10.3)	33.7(10.9)	40.3(8.6)	36.9(11.6)	36.2(10.1)		
Non-Paretic	50(8.9)	52.5(9.0)	46.4(7.9)	50.1(9.8)	49.9(8.9)		
Toe-out angle (°)						15.47(5.83)	14.68(6.77)
Paretic	16.6(13.9)	19.1(9.7)	13.1(18.7)	12.6(19.9)	18.8(9.8)		
Non-Paretic	15.5(7.5)	14.8(7.3)	16.5 (8.1)	18.2(3.6)	14.0(8.7)		

4.3.3 All stroke survivors Knee adduction moment (KAM).

4.3.3.1 KAM Differences at Varying Speeds in Healthy Adults

The magnitude of peak KAM was significantly lower ($f(1,17)=15.6$, $p=001$, $EF=0.52$) at a slow walking speed (0.8 m/s) than at SS walking speeds (see Figure 4-1a). In contrast, the KAM impulse was significantly greater ($f(1,17)=52.4$, $p=000$, $EF=0.83$) at a slower walking speed (see Figure 4-1b).

4.3.3.2 KAM Differences among the Stroke Survivors (between Paretic and Non-paretic Sides)

There were no significant differences between the stroke survivors' paretic and non-paretic sides in any measure of KAM (peak KAM and KAM impulse) (see Figure 4-1a-b).

4.3.3.3 Stroke Survivors versus Healthy Participants Walking at SS (Covariate SS Speed: ANCOVA) and Slow (0.8 m/s: ANOVA) Speeds

When covarying for walking speed, only KAM impulse was found to be significantly lower on the paretic side, compared to the healthy participants at SS walking speeds ($f(1,32)=10.22$, $p<0.003$, EF=0.42; see Figure 4-1a-b). No other KAM measures were significantly different (all means and SDs are reported in Table 4-2).

When comparing the knee joint moments of healthy individuals with those of the stroke survivors walking at 0.8m/s, no differences were found in peak KAM. However, KAM impulse on both the NP and P sides was significantly lower than in the healthy participants ($f(1.33)= 11.83$, $p<0.002$, ES=1.13 for P and $f(1,33)= 10.37$, $p=0.003$, ES= 0.85 for NP; see Figure 4-1a-b; all means and SDs are reported in Table 4-2).

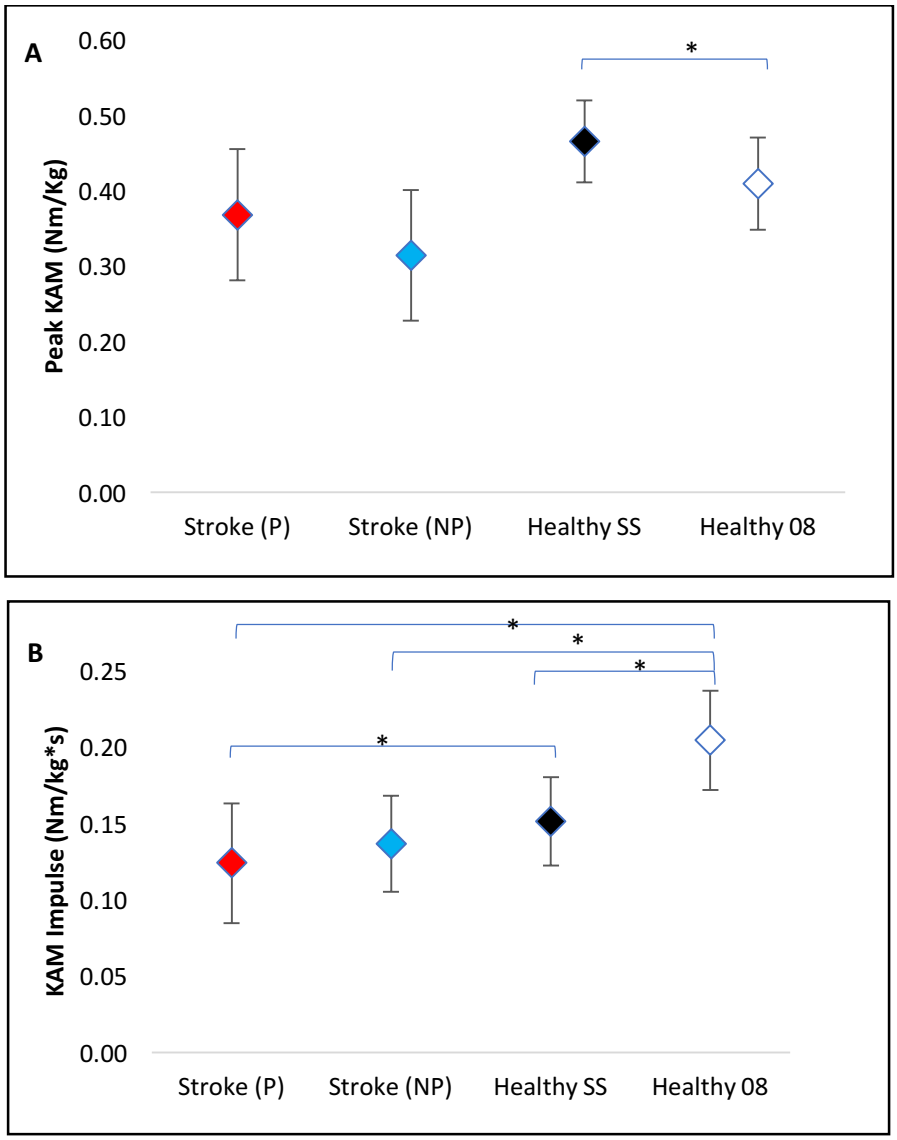


Figure 4-1: Observed knee joint moments in healthy controls, compared to stroke survivors walking at SS speeds. Observed means are represented by boxes, and 95% confidence intervals by whiskers for healthy participants (walking at SS speeds [black] and 0.8 m/s [white]) and stroke survivors on the non-paretic (NP: blue) and paretic sides (P: red), with regard to: A) peak KAM, and B) KAM impulse. *Significant difference (P<0.05).

Table 4-2: Observed means (SD) of peak KAM and KAM impulse in stroke survivors (n=17) and healthy controls (n=18), walking at SS speeds. *Number of stroke survivors whose mean joint moments exceeded the upper boundaries of a 95% confidence interval in the cohort of healthy participants walking at SS speeds and 0.8 m/s.

	HEALTHY (SS)	HEALTHY (0.8)	STROKE (paretic)	*Number exceeding moments of healthy controls (paretic).		STROKE (non-paretic)	*Number exceeding moments of healthy controls (non-paretic).	
				SS	0.8 m/s		SS	0.8 m/s
Peak KAM (Nm/kg)	0.47(0.11)	0.41 (0.12)	0.37 (0.17)	3	4	0.31 (0.17)	1	2
KAM IMPULSE (Nm/kg*s)	0.15(0.06)	0.2(0.06)	0.12(0.08)	2	2	0.14(0.06)	4	1

Table 4-3: KAM effect size estimations

Test	Effect Size Cohen's *d* (95% CI)
STROKE:	
Peak KAM Paretic –Non-Paretic sides	0.35(-0.33-1.03)
KAM Impulse Paretic –Non-Paretic sides	0.28(-0.4-0.96)
HEALTHY-STROKE (ANCOVA; SS Speed):	
Peak KAM Healthy –Paretic side	0.70(0.02-1.38)
Peak KAM Healthy –Non-Paretic side	1.11(0.40-1.82)
KAM Impulse Healthy –Paretic side	0.42(-0.25-1.09)
KAM Impulse Healthy –Non-Paretic side	0.17(-0.49-0.83)
HEALTHY-STROKE (ANOVA; 0.8 m/s Speed):	
Peak KAM Healthy –Paretic side	0.27(-0.40-0.94)
Peak KAM Healthy –Non-Paretic side	0.68(0.00-1.36)
KAM Impulse Healthy –Paretic side	1.13(0.42-1.84)
KAM Impulse Healthy –Non-Paretic side	0.85(0.16-1.54)

4.3.4 Knee Flexion Moment (KFM) in All the Stroke Survivors

4.3.4.1 KFM Variation at Different Speeds in Healthy Participants

The magnitude of the KFM peak was significantly lower ($f(1,17)=37.06$, $p<000$, ES= 1.16) at a slow speed (0.8 m/s) than at SS walking speeds (see Figure 4-2).

4.3.4.2 KFM Differences among the Stroke Survivors (between Paretic and Non-paretic Sides)

No significant differences in KFM were found between sides in the group of stroke survivors (see Figure 4-2).

4.3.4.3 Stroke Survivors versus Healthy Participants Walking at SS (Covariate SS Speed: ANCOVA) and Slow (0.8 m/s: ANOVA) Speeds

For the stroke survivors, KFM was significantly higher on the non-paretic side ($f(1,33)=5.62$, $p=0.024$, ES=0.81), compared to the healthy controls walking at a slow matched speed of 0.8 m/s. However, there was no significant difference at SS walking speeds (see Figure 4-2; all means and SDs are reported in Table 4-4).

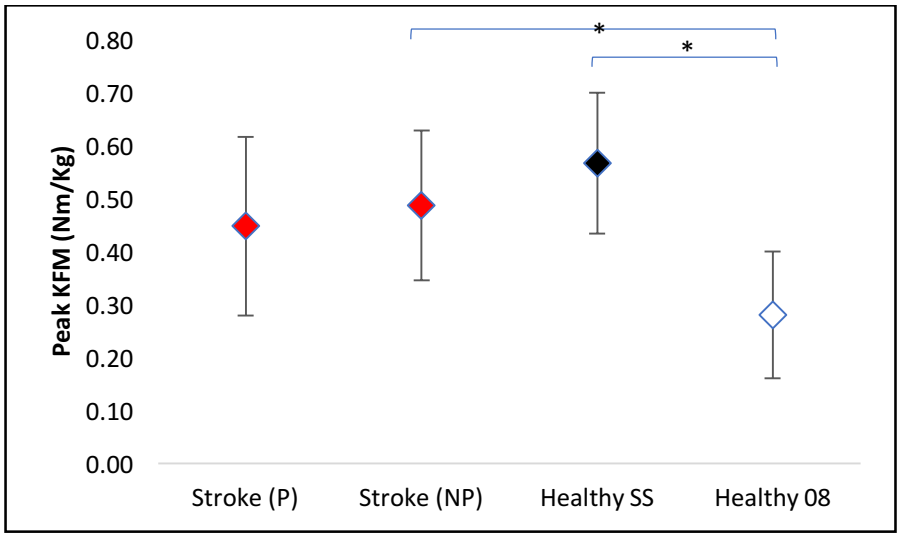


Figure 4-2: Observed knee joint moments in healthy controls, compared to those of stroke survivors walking at SS speeds. Observed means are represented by boxes, and 95% confidence intervals by whiskers for the healthy participants (walking at SS [black] speeds and 0.8 m/s [white]), and stroke survivors on the non-paretic (NP: blue) and paretic sides (P: red), with regard to peak KFM. *Significant difference (P<0.05)

Table 4-4: Observed means (SD) of KFM in stroke survivors (n=17) and healthy controls (n=18), walking at SS speeds. *Numbers of stroke survivors whose mean joint moments exceeded the upper boundaries of a 95% confidence interval in the cohort of healthy participants walking at SS speeds and 0.8 m/s.

	HEALTHY (SS)	HEALTHY (0.8)	STROKE (paretic)	* *Number exceeding moments of healthy controls (paretic).*		STROKE (non-paretic)	* *Number exceeding moments of healthy controls (non-paretic).*	
				SS	0.8 m/s		SS	0.8 m/s
Peak KFM (Nm/kg)	0.57(0.26)	0.28 (0.24)	0.45 (0.33)	3	8	0.49 (0.28)	3	9

Table 4-5: KFM effect size estimations**.**

Test	Effect Size Cohen's *d* (95% CI)
HEALTHY:	
Peak KFM SS - 0.8 m/s	1.16(0.45-1.87)
STROKE:	
Peak KFM Paretic –Non-Paretic sides	0.13(-0.54-0.80)
HEALTHY-STROKE (ANCOVA; SS Speed):	
Peak KFM Healthy –Paretic side	0.40(-0.27-1.07)
Peak KFM Healthy –Non-Paretic side	0.30(-0.37-0.97)
HEALTHY-STROKE (ANOVA; 0.8 m/s Speed):	
Peak KFM Healthy –Paretic side	0.59(-0.09-1.27)
Peak KFM Healthy –Non-Paretic side	0.81(0.12-1.50)

4.3.5 KAM in Sub-groups of Stroke Survivors

4.3.5.1 KAM in Temporal Symmetry/Asymmetry Sub-groups of Stroke Survivors (between Paretic and Non-paretic Sides)

Compared to the whole cohort of stroke survivors, asymmetry between the paretic and non-paretic sides of peak KAM was 19% higher in the ***temporal asymmetry*** sub-group. In contrast, peak KAM asymmetry was 8% lower in the ***temporal symmetry*** sub-group, compared to the entire cohort of stroke survivors (see Figure 4-3).

The asymmetry in KAM impulse between the paretic and non-paretic sides in the ***temporal asymmetry*** sub-group was comparable to the whole cohort of stroke survivors. However, asymmetric KAM impulse in the ***temporal symmetry*** sub-group was 17% higher than in the cohort as a whole (see Figure 4-4).

4.3.5.2 KAM in the Spatial Symmetry/Asymmetry Sub-groups of Stroke Survivors (between Paretic and Non-paretic Sides)

Peak KAM asymmetry was 6% lower in the ***spatial asymmetry*** sub-group, compared to the whole cohort of stroke survivors. In contrast, peak KAM asymmetry in the ***spatial symmetry*** sub-group was comparable to the whole cohort of stroke survivors (see Figure 4-3).

Meanwhile, KAM impulse asymmetry between the paretic and non-paretic sides of the ***spatial asymmetry*** sub-group was 4% higher than in the entire cohort of stroke survivors. In contrast, the KAM impulse asymmetry of the ***spatial symmetry*** sub-group was 8.5% lower than in the entire cohort (see Figure 4-4).

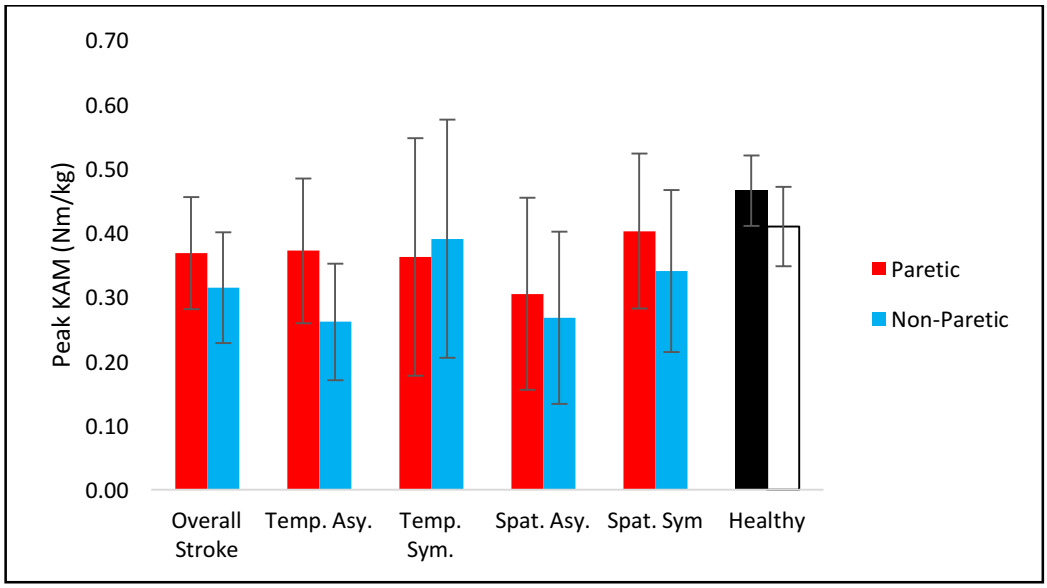


Figure 4-3: Observed means of peak KAM on the paretic (P: red) and non-paretic (NP: blue) sides among the stroke survivors (n=17), sub-group of stroke survivors with temporal asymmetry (asymmetrical group [n=10], symmetrical group [n=7]), sub-groups of stroke survivors with spatial asymmetry (asymmetrical group [n=6], symmetrical group [n=11]), and healthy controls (n=18), walking at two different speeds: SS (black) and 0.8 m/s (white). Error bars indicate 95% confidence intervals, illustrated by whiskers.

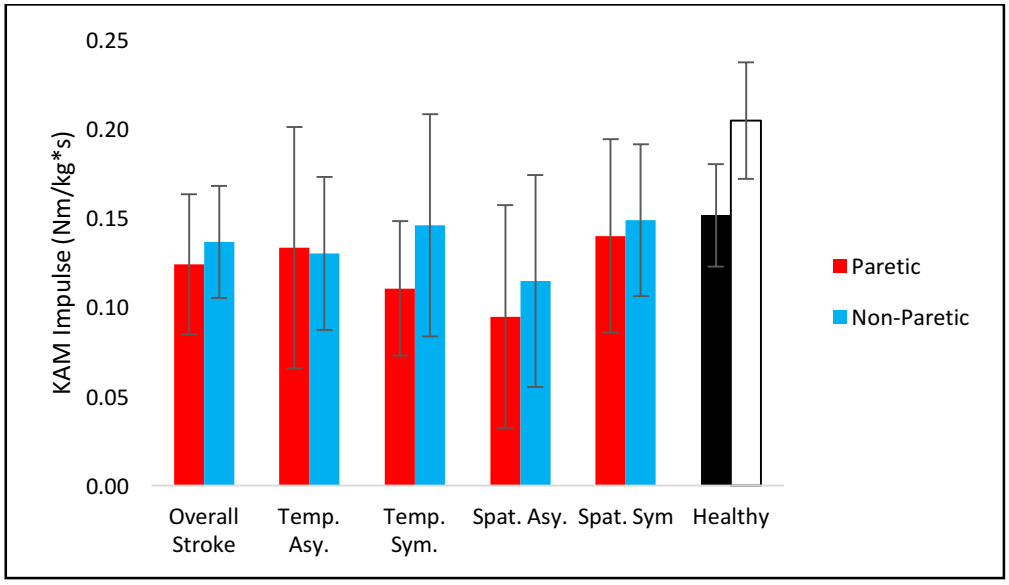


Figure 4-4: Observed means of KAM impulse on paretic (P: red) and non-paretic (NP: blue) sides among the stroke survivors (n=17), sub-group of stroke survivors with temporal asymmetry (asymmetrical group [n=10], symmetrical group [n=7]), sub-groups of stroke survivors with spatial asymmetry (asymmetrical group [n=6], symmetrical group [n=11]), and healthy controls (n=18), walking at two different speeds: SS (black) and 0.8 m/s (white). Error bars indicate 95% confidence intervals, illustrated by whiskers.

4.3.5.3 Temporal Symmetry/Asymmetry Sub-groups of Stroke Survivors versus Healthy Participants Walking at SS Speeds and 0.8 m/s

In the ***temporal asymmetry*** sub-group of stroke survivors, peak KAM on the paretic side was comparable to that of the healthy controls walking at 0.8 m/s, but lower than in the healthy controls walking at SS speeds. However, the peak KAM of the non-paretic side was 70% lower than in the healthy controls, and 90% of the stroke survivors exceeded the lower 95% CI of the healthy controls walking at 0.8 m/s and SS speeds, respectively (see Figure 4-5a; Table 4-6).

KAM impulse on the paretic and non-paretic sides of the ***temporal asymmetry*** sub-group was comparable to that of the healthy controls walking at SS speeds. However, KAM impulse on the paretic and non-paretic sides was lower than in the healthy controls walking at 0.8 m/s, with most of the stroke survivors exceeding the lower 95% CI limit (see Figure 4-5b; Table 4-6).

In the ***temporal symmetry*** sub-group of stroke survivors, peak KAM on the paretic and non-paretic sides was comparable to that of the healthy controls walking at 0.8 m/s. In contrast, peak KAM on the paretic side was lower, compared to the lower 95% CI of the healthy controls walking at SS speeds. However, most of the stroke survivors exceeded the lower 95% CI of the healthy controls (see Figure 4-5a; Table 4-6).

KAM impulse on the paretic and non-paretic sides of the ***temporal symmetry*** sub-group of stroke survivors was lower than in the healthy controls walking at 0.8 m/s, and most of the stroke survivors exceeded the lower 95% CI limit. However, while the KAM impulse of the ***temporal symmetry*** sub-group on the non-paretic side was comparable to that of the healthy controls walking at SS speeds, KAM impulse on the paretic side was lower than the 95% CI of the healthy controls walking at SS speeds (see Figure 4-5b; Table 4-6).

Table 4-6: Mean (SD) of peak KAM and KAM impulse in ***temporal*** sub-groups of stroke survivors (temporal asymmetry [n=10] and temporal symmetry [n=7]) and healthy controls (n=18) walking at SS speeds.

		Stroke		Healthy	
		Paretic	Non-paretic	SS	0.8 m/s
Asymmetrical group	**Peak KAM (Nm/kg)**	0.37 (0.16)	0.26 (0.13)	0.47(0.11)	0.41 (0.12)
	KAM IMPULSE (Nm/kg*s)	0.13(0.09)	0.13(0.06)	0.15(0.06)	0.20(0.06)
Symmetrical group	**Peak KAM (Nm/kg)**	0.36(0.20)	0.39(0.20)	0.47(0.11)	0.41 (0.12)
	KAM IMPULSE (Nm/kg*s)	0.11(0.04)	0.15(0.07)	0.15(0.06)	0.20(0.06)

Table 4-7: KAM effect size estimations in temporal sub-groups**.**

Test	Effect Size Cohen's *d* (95% CI)
ASYMMETRICAL STROKE:	
Peak KAM Paretic –Non-Paretic sides	0.75(-0.16-1.66)
KAM Impulse Paretic –Non-Paretic sides	0.00(-0.88-0.88)
HEALTHY-ASYMMETRICAL STROKE (SS Speed):	
Peak KAM Healthy –Paretic side	0.73(-0.07-1.53)
Peak KAM Healthy –Non-Paretic side	1.74(0.84-2.64)
KAM Impulse Healthy –Paretic side	0.26(-0.52-1.04)
KAM Impulse Healthy –Non-Paretic side	0.33(-0.45-1.11)
HEALTHY-ASYMMETRICAL STROKE (0.8 m/s Speed):	
Peak KAM Healthy –Paretic side	0.28(-0.50-1.06)
Peak KAM Healthy –Non-Paretic side	1.20(0.37-2.03)
KAM Impulse Healthy –Paretic side	0.92(0.11-1.73)
KAM Impulse Healthy –Non-Paretic side	1.67(0.78-2.56)
SYMMETRICAL STROKE:	
Peak KAM Paretic –Non-Paretic sides	0.15(-0.90-1.20)
KAM Impulse Paretic –Non-Paretic sides	0.70(-0.38-1.78)
HEALTHY-SYMMETRICAL STROKE (SS Speed):	
Peak KAM Healthy –Paretic side	0.68(-0.21-1.57)
Peak KAM Healthy –Non-Paretic side	0.50(-0.38-1.38)
KAM Impulse Healthy –Paretic side	0.78(-0.12-1.68)
KAM Impulse Healthy –Non-Paretic side	0.00(-0.87-0.87)
HEALTHY-SYMMETRICAL STROKE (0.8 m/s Speed):	
Peak KAM Healthy –Paretic side	0.30(-0.58-1.18)
Peak KAM Healthy –Non-Paretic side	0.12(-0.75-0.99)
KAM Impulse Healthy –Paretic side	0.18(-0.69-1.05)
KAM Impulse Healthy –Non-Paretic side	0.77(-0.13-1.67)

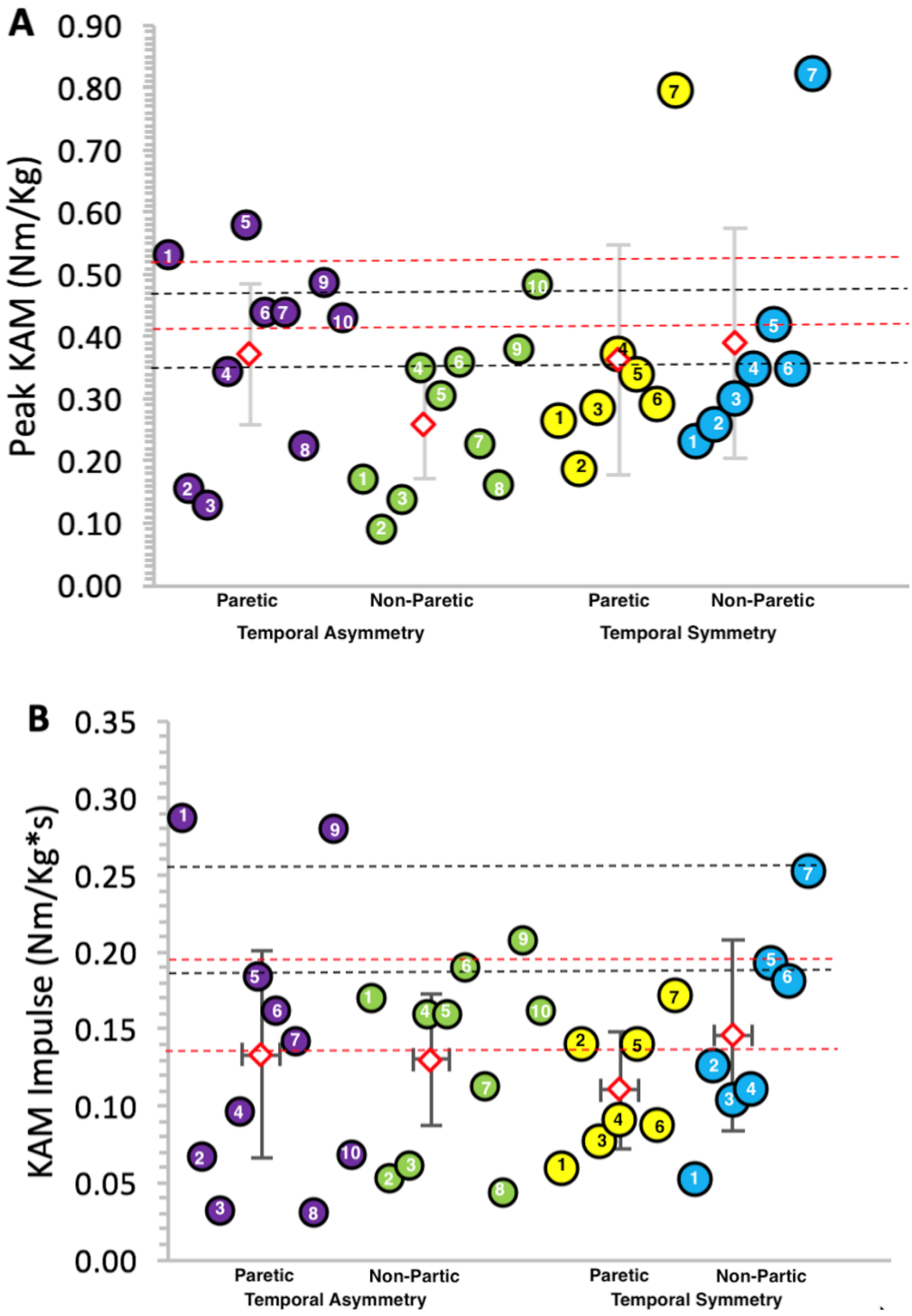


Figure 4-5: Observed mean knee joint moments and 95% confidence intervals, indicated by whiskers for temporal sub-groups of stroke survivors (asymmetrical and symmetrical groups). The stroke survivors' individual means are represented by scatter plots (numbered), referring to the paretic and non-paretic sides in relation to: A) peak KAM, and B) KAM impulse. Horizontal lines represent the observed upper and lower limits of 95% confidence intervals for the healthy controls (n=18), walking at slow (0.8 m/s: black) and SS (red) speeds.

4.3.5.4 Spatial Symmetry/Asymmetry Sub-groups of Stroke Survivors versus Healthy Participants Walking at SS Speeds and 0.8 m/s

In ***spatial asymmetry*** sub-groups of stroke survivors, peak KAM on the paretic and non-paretic sides was found to be lower than the lower 95% CI of healthy controls walking at 0.8 m/s and SS speeds. However, while KAM impulse on the non-paretic side in the ***spatial asymmetry*** sub-group was comparable to that of the healthy controls walking at SS speeds, the paretic side was lower, compared to the lower 95% CI of the healthy controls walking at SS speeds (see Figure 4-6 a-b; Table 4-8).

In the ***spatial symmetry*** sub-group of stroke survivors, peak KAM on the paretic side was comparable to that of healthy controls walking at 0.8 m/s, but lower than the lower 95% CI of the healthy controls walking at SS speeds. In contrast, peak KAM of the non-paretic side was lower than the lower 95% CI of the healthy controls walking at 0.8 m/s and SS speeds. However, in more than 60% of the stroke survivors, the paretic and non-paretic sides exceeded the lower 95% CI of the healthy controls walking at 0.8 m/s and SS speeds (see Figure 4-6a; Table 4-8).

KAM impulse on the paretic and non-paretic sides in the ***spatial symmetry*** sub-group of stroke survivors was lower than in healthy controls walking at 0.8 m/s, and most of the stroke participants exceeded the lower 95% CI limit. However, KAM impulse on the non-paretic side in the ***spatial symmetry*** sub-group was comparable to that of the healthy controls walking at SS speeds (see Figure 4-6b; Table 4-8).

Table 4-8: Observed means (SD) of KAM and KAM impulse in the spatial sub-groups of stroke survivors (spatial asymmetry [n=6] and spatial symmetry [n=11]) and healthy controls (n=18), walking at SS speeds.

		Stroke		Healthy	
		Paretic	Non-paretic	*SS*	0.8 m/s
Asymmetrical group	**Peak KAM (Nm/kg)**	0.30 (0.14)	0.27 (0.13)	0.47(0.11)	0.41 (0.12)
	KAM IMPULSE (Nm/kg*s)	0.09(0.06)	0.11(0.06)	0.15(0.06)	0.20(0.06)
Symmetrical group	**Peak KAM (Nm/kg)**	0.40(0.18)	0.34(0.19)	0.47(0.11)	0.41 (0.12)
	KAM IMPULSE (Nm/kg*s)	0.14(0.08)	0.15(0.06)	0.15(0.06)	0.20(0.06)

Table 4-9: KAM effect size estimations in spatial sub-groups**.**

Test	Effect Size Cohen's *d* (95% CI)
ASYMMETRICAL STROKE:	
Peak KAM Paretic –Non-Paretic sides	0.22(-0.92-1.36)
KAM Impulse Paretic –Non-Paretic sides	0.33(-0.81-1.47)
HEALTHY-ASYMMETRICAL STROKE (SS Speed):	
Peak KAM Healthy –Paretic side	1.35(0.35-2.35)
Peak KAM Healthy –Non-Paretic side	1.66(0.62-2.70)
KAM Impulse Healthy –Paretic side	1.00 (0.03-1.97)
KAM Impulse Healthy –Non-Paretic side	0.67(-0.27-1.61)
HEALTHY-ASYMMETRICAL STROKE (0.8 m/s Speed):	
Peak KAM Healthy –Paretic side	0.84(-0.11-1.79)
Peak KAM Healthy –Non-Paretic side	1.12(0.14-2.10)
KAM Impulse Healthy –Paretic side	1.83(0.77-2.89)
KAM Impulse Healthy –Non-Paretic side	1.50(0.48-2.52)
SYMMETRICAL STROKE:	
Peak KAM Paretic –Non-Paretic sides	0.41(-0.43-1.25)
KAM Impulse Paretic –Non-Paretic sides	0.14(-0.70-0.98)
HEALTHY-SYMMETRICAL STROKE (SS Speed):	
Peak KAM Healthy –Paretic side	0.47(-0.29-1.23)
Peak KAM Healthy –Non-Paretic side	0.83 (0.05-1.61)
KAM Impulse Healthy –Paretic side	0.14(-0.61-0.89)
KAM Impulse Healthy –Non-Paretic side	0.00(-0.75-0.75)
HEALTHY-SYMMETRICAL STROKE (0.8 m/s Speed):	
Peak KAM Healthy –Paretic side	0.07(-0.68-0.82)
Peak KAM Healthy –Non-Paretic side	0.44(-0.32-1.20)
KAM Impulse Healthy –Paretic side	0.85(0.07-1.63)
KAM Impulse Healthy –Non-Paretic side	0.83(0.05-1.61)

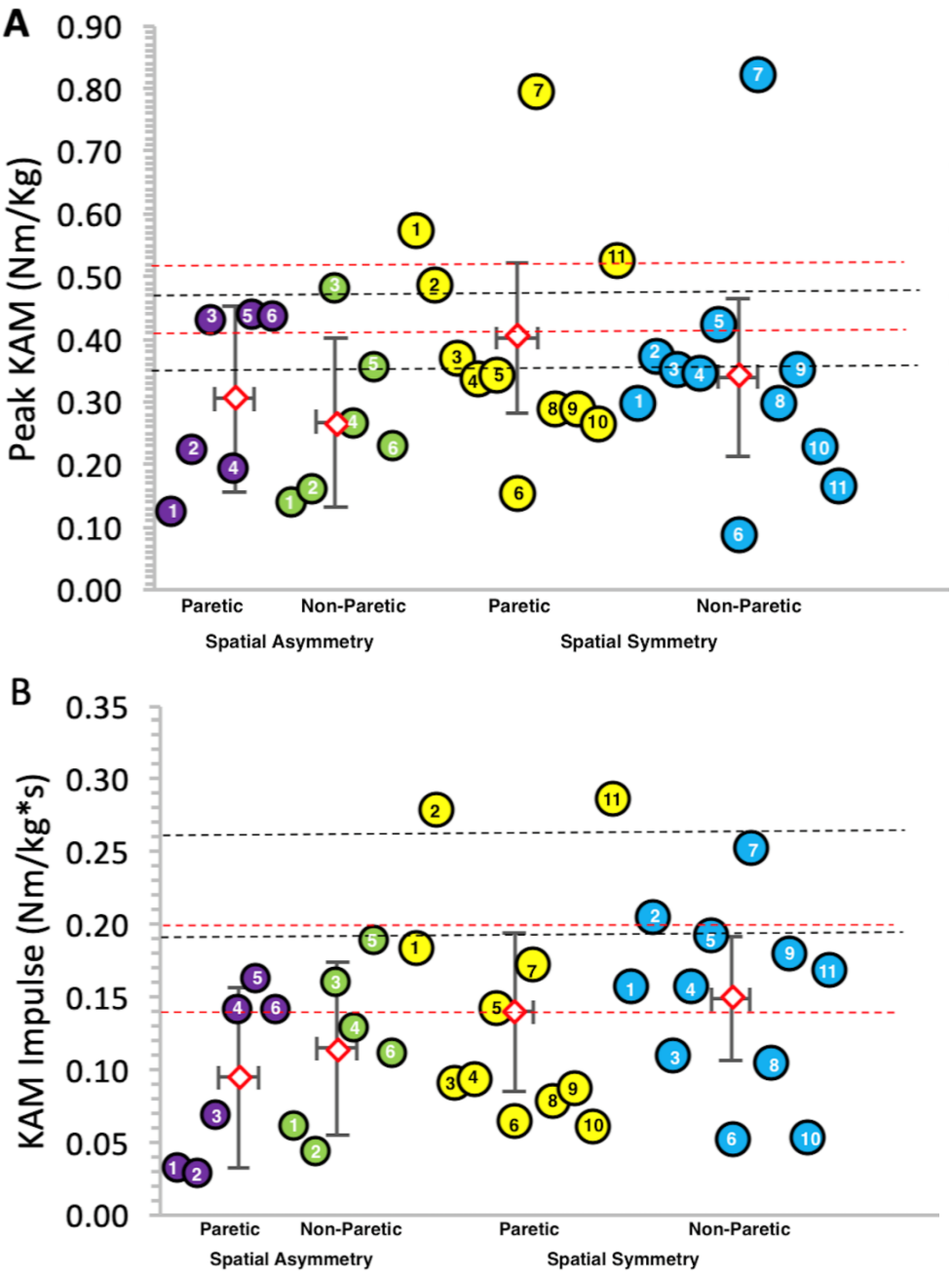


Figure 4-6: Observed means of knee joint moments and 95% confidence intervals, indicated by whiskers for the spatial sub-groups of stroke survivors (asymmetrical and symmetrical groups). The stroke survivors' individual means are represented by scatter plots (numbered) for the paretic and non-paretic sides, with regard to: A) peak KAM, and B) KAM impulse. Horizontal lines represent the observed upper and lower limits of 95% confidence intervals for the healthy controls (n=18), walking at slow (0.8 m/s: black) and SS (red) speeds.

4.3.6 Knee Flexion Moment (KFM) in Sub-groups of Stroke Survivors

4.3.6.1 KFM in Temporal Symmetry/Asymmetry Sub-groups of Stroke Survivors (between Paretic and Non-paretic Sides)

Compared to the whole cohort of stroke survivors, the peak KAM asymmetry between the paretic and non-paretic sides was 27% higher in the ***temporal asymmetry*** sub-group. In contrast, peak KFM symmetry in the ***temporal symmetry*** sub-group was comparable to the whole cohort of stroke survivors (see Figure 4-7).

4.3.6.2 KFM in Spatial Symmetry/Asymmetry Sub-groups of Stroke Survivors (between Paretic and Non-paretic Sides)

Peak KFM asymmetry between the paretic and non-paretic sides was 9% higher in the ***spatial asymmetry*** sub-group than in the whole cohort of stroke survivors. In contrast, peak KFM asymmetry in the ***spatial symmetry*** sub-group was comparable to the whole cohort of stroke survivors (see Figure 4-7).

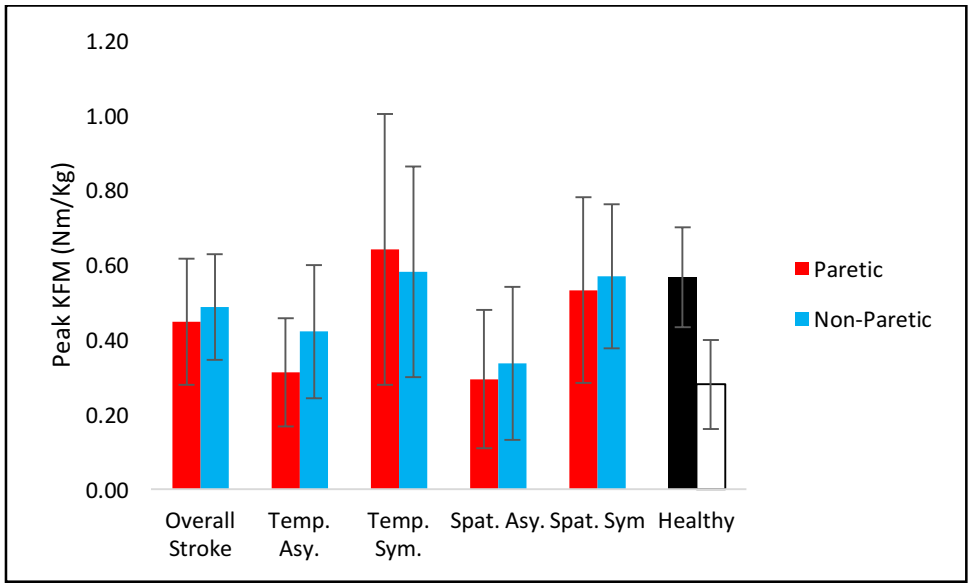


Figure 4-7: Observed means of KFM on the paretic (P: red) and non-paretic (NP: blue) sides among the stroke survivors (n=17), the sub-groups of stroke survivors with temporal asymmetry (asymmetrical group: n=10, symmetrical group: n=7), sub-groups of stroke survivors with spatial asymmetry (asymmetrical group: n=6, symmetrical group: n=11), and healthy controls: n=18), walking at two different speeds: SS (black) and 0.8 m/s (white). Error bars indicate 95% confidence intervals, illustrated by whiskers.

4.3.6.3 Temporal Symmetry/Symmetry Sub-groups of Stroke Survivors versus Healthy Participants Walking at SS Speeds and 0.8 m/s

In the ***temporal asymmetry*** sub-group of stroke survivors, peak KFM on the paretic side was comparable to that of healthy controls walking at 0.8 m/s, but lower than in healthy controls walking at SS speeds. However, peak KFM on the non-paretic side was lower than that of healthy controls walking at SS speeds, and higher than in healthy controls walking at 0.8 m/s. Meanwhile, in 70% of the stroke survivors, the paretic and non-paretic sides exceeded the lower 95% CI of the healthy controls walking at SS speeds (see Figure 4-8; Table 4-10).

In the ***temporal symmetry*** sub-group of stroke survivors, peak KFM on the paretic and non-paretic sides was comparable to that of healthy controls walking at SS speeds. However, peak KFM on both sides (paretic and non-paretic) was higher than the upper 95% CI of healthy controls walking at 0.8 m/s. Meanwhile, for both the paretic and non-paretic sides, 71% and 43% of the ***temporal symmetry*** sub-group exceeded the upper 95% CI of the healthy controls walking at 0.8 m/s and SS speeds, respectively (see Figure 4-8; Table 4-10).

Table 4-10: Observed means (SD) of KFM in the temporal sub-groups of stroke survivors (temporal asymmetry [n=10] and temporal symmetry [n=7]) and healthy controls (n=18), walking at SS speeds and 0.8 m/s.

		Stroke		Healthy	
		Paretic	**Non-paretic**	***SS***	**0.8 m/s**
Asymmetrical group	**Peak KFM (Nm/kg)**	0.31 (0.20)	0.42 (0.25)	0.57(0.26)	0.28 (0.24)
Symmetrical group	**Peak KFM (Nm/kg)**	0.64(0.39)	0.58(0.30)		

Table 4-11: KFM effect size estimations in temporal sub-groups.

Test	Effect Size Cohen's *d* (95% CI)
ASYMMETRICAL STROKE:	
Peak KFM Paretic –Non-Paretic sides	0.49(-0.40-1.38)
SYMMETRICAL STROKE:	
Peak KFM Paretic –Non-Paretic sides	0.17(-0.88-1.22)
HEALTHY-ASYMMETRICAL STROKE (SS Speed):	
Peak KFM Healthy –Paretic side	1.12(0.29-1.95)
Peak KFM Healthy –Non-Paretic side	0.59(-0.20-1.38)
HEALTHY-ASYMMETRICAL STROKE (SS Speed):	
Peak KFM Healthy –Paretic side	0.21(-0.56-0.98)
Peak KFM Healthy –Non-Paretic side	0.40(-0.38-1.18
HEALTHY-SYMMETRICAL STROKE (0.8 m/s Speed):	
Peak KFM Healthy –Paretic side	0.14(-0.73-1.01)
Peak KFM Healthy –Non-Paretic side	0.57(-0.32-1.46)
HEALTHY-SYMMETRICAL STROKE (0.8 m/s Speed):	
Peak KFM Healthy –Paretic side	1.11(0.18-2.04)
Peak KFM Healthy –Non-Paretic side	1.10(0.18-2.02)

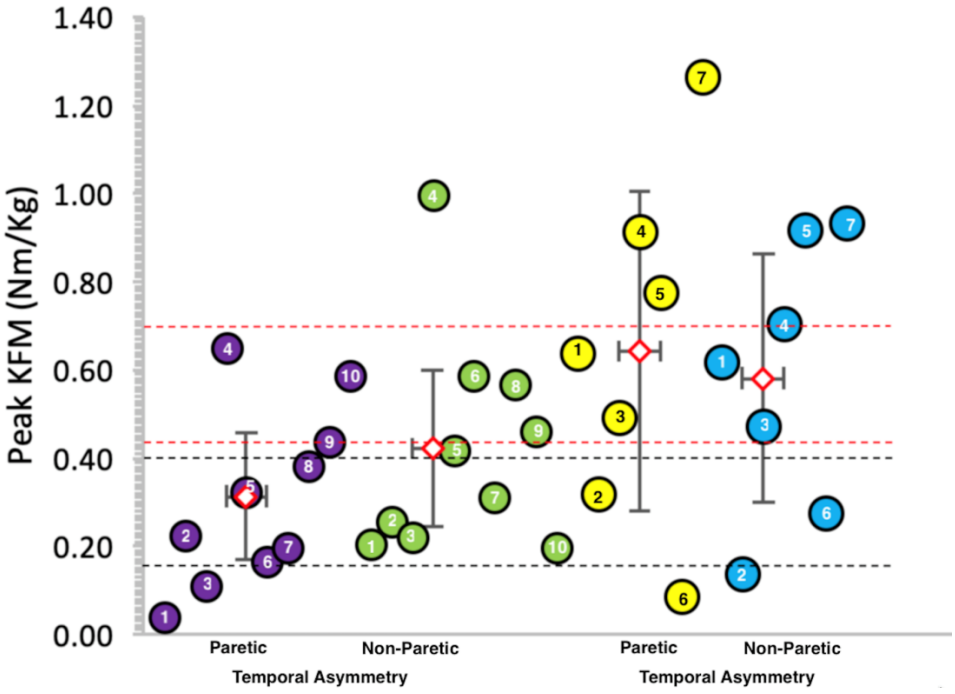


Figure 4-8: Mean peak KFM and 95% confidence intervals, indicated by whiskers for the temporal sub-groups of stroke survivors (asymmetrical and symmetrical groups). The stroke survivors' individual means are represented by scatter plots (numbered) for the paretic and non-paretic sides. Horizontal lines represent the observed upper and lower limits of 95% confidence intervals among the healthy controls (n=18), walking at slow (0.8 m/s: black) and SS (red) speeds.

4.3.6.4 Spatial Symmetry/Asymmetry Sub-groups of Stroke Survivors versus Healthy Participants Walking at SS Speeds and 0.8 m/s

In the ***spatial asymmetry*** sub-groups of stroke survivors, peak KFM on the paretic and non-paretic sides was comparable to that of healthy controls walking at 0.8 m/s and SS speeds. However, in the ***spatial symmetry*** sub-group of stroke survivors, peak KFM on the paretic and non-paretic sides was comparable to that of the healthy controls walking at 0.8 m/s and SS speeds. In contrast, while over 20% of the ***spatial symmetry*** sub-group exceeded the upper 95% CI of the healthy controls for both sides walking at SS speeds, 60% of the participants exceeded the upper 95% CI of the healthy controls walking at 0.8 m/s (see Figure 4-9; Table 4-12).

Table 4-12: Observed means (SD) of KFM in the spatial sub-groups of stroke survivors (spatial asymmetry [n=6] and spatial symmetry [n=11]) and healthy controls (n=18), walking at SS speeds and 0.8 m/s

		Stroke		Healthy	
		Paretic	**Non-paretic**	***SS***	**0.8 m/s**
Asymmetrical group	**Peak KFM (Nm/kg)**	0.29 (0.18)	0.34 (0.19)	0.57(0.26)	0.28 (0.24)
Symmetrical group	**Peak KFM (Nm/kg)**	0.53(0.37)	0.57(0.29)		

Table 4-13: KFM effect size estimations in spatial sub-groups**.**

Test	Effect Size Cohen's *d* (95% CI)
ASYMMETRICAL STROKE:	
Peak KFM Paretic –Non-Paretic sides	0.27(-0.87-1.41)
SYMMETRICAL STROKE:	
Peak KFM Paretic –Non-Paretic sides	0.12(-0.72-0.96)
HEALTHY-ASYMMETRICAL STROKE (SS Speed):	
Peak KFM Healthy –Paretic side	1.25(0.26-2.24)
Peak KFM Healthy –Non-Paretic side	1.01(0.04-1.98)
HEALTHY-ASYMMETRICAL STROKE (SS Speed):	
Peak KFM Healthy –Paretic side	0.13(-0.79-1.05)
Peak KFM Healthy –Non-Paretic side	0.00(-0.92-0.92)
HEALTHY-SYMMETRICAL STROKE (0.8 m/s Speed):	
Peak KFM Healthy –Paretic side	0.05(-0.70-0.80)
Peak KFM Healthy –Non-Paretic side	0.28(-0.47-1.03)
HEALTHY-SYMMETRICAL STROKE (0.8 m/s Speed):	
Peak KFM Healthy –Paretic side	0.80(0.02-1.58)
Peak KFM Healthy –Non-Paretic side	1.09(0.29-1.89)

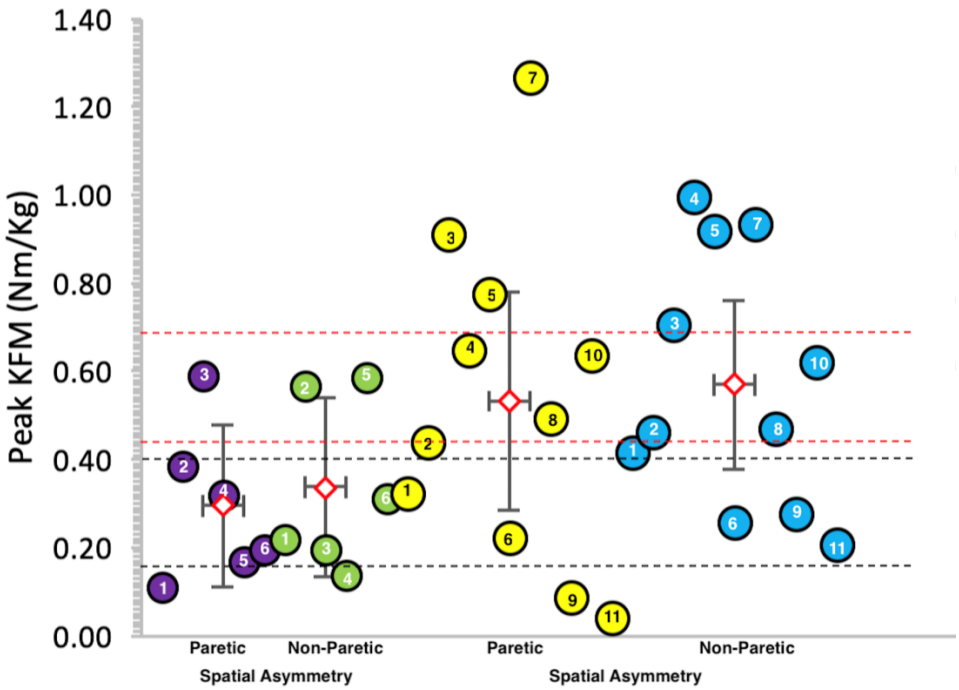


Figure 4-9: Observed means of peak KFM and 95% confidence intervals, indicated by whiskers for the spatial sub-groups of stroke survivors (asymmetrical and symmetrical groups). The individual stroke survivors' means are represented by scatter plots (numbered) for the paretic and non-paretic sides. Horizontal lines represent the observed upper and lower limits of the 95% confidence intervals for the healthy controls (n=18), walking at slow (0.8 m/s: black) and SS (red) speeds.

4.4 Discussion

To the author's knowledge, this is the first study to characterise knee joint moment patterns in stroke survivors (reflecting joint loading patterns that are prognostic of the risk of joint degeneration). Moreover, it is believed to be the first study to measure KAM and KFM in sub-groups of stroke survivors with severe temporal or spatial asymmetry. This is important, because an understanding of joint loading and how this changes after stroke can help clinicians prioritise gait rehabilitation goals (for example, to correct symmetry during walking), in order to limit the potential for long-term knee joint degeneration.

The results of this study indicate that the KAM on both the paretic and non-paretic sides was lower in long-term stroke survivors (with or without spatiotemporal gait asymmetry), compared to their healthy counterparts. This may be due to compensatory gait patterns, such as hip hiking. However, KFM on the non-paretic side in the majority (52%) of the stroke survivors exceeded that of the healthy controls, when walking at matched slow speeds. This may present a risk of joint degeneration, given that heightened KFM is linked to increased patellofemoral joint contact stress, as well as the risk of patellofemoral pain and future patellofemoral OA (Creaby et al., 2013; Farrokhi et al., 2015). The results of this study were therefore examined with a view to understanding how compensatory patterns and the severity of asymmetrical spatiotemporal gait patterns, which are common after stroke, may explain the knee joint moments observed and determine whether some individuals could be at greater risk of high joint moment than others. Importantly, all the significant differences of this study, either within or between groups, were above the reported SEM values (less than 3.7% and 8.7% for KAM and KFM, respectively), presented in 3.8.

4.4.1 Knee Joint Moment Asymmetry between Sides in Healthy Participants and Stroke Survivors

Knee Joint Moment at Different Speeds in Healthy Participants

External knee joint moments (reflected in KAM and KFM) are used as surrogate measures of loading, with established associations between increased peak KAM and KFM, and a heightened risk of developing OA (Chehab et al., 2014; Thorp et al., 2006). However, walking speed plays an important role in altering knee joint moment. Thus, KAM impulse (loading over

the duration of the stance phase) is thought to be a more sensitive predictor of OA risk than peak moments (de David et al., 2015; Robbins and Maly, 2009).

Knee joint moments (peak and impulse) are affected by changes in walking speed. According to Robbins and Maly (2009), knee impulse is more sensitive to changes in walking speed than the magnitude of KAM peaks in healthy participants. The results of the above-mentioned study showed that an increase in KAM impulse and KAM peaks was due to slow walking speed (thus increasing stance duration) and an increase in speed, respectively. The results of the current study are consistent with Robbins and Maly (2009), as the healthy participants demonstrated a significantly increased KAM peak and decreased KAM impulse, while walking at SS as opposed to slow speeds. When the healthy participants in the current study were asked to walk at a slower speed, this decreased their KFM. Again, this is consistent with the findings of van den Noort et al. (2013), who reported that KFM decreased with slower walking speeds.

In consideration of the findings of this study, the effect of walking speed on knee joint moments should be taken into account in clinical gait studies. Accordingly, as individuals with pathology tend to walk slower than healthy subjects (Fey and Neptune, 2012; Zeni and Higginson, 2009), walking speed should be accounted for in the discrepancies between pathological and healthy populations, with regard to joint moment/loading (Telfer et al., 2017).

Impact Statements:

Knee joint moments are affected by walking speed. Decreasing walking speed will also decrease peak moments (KAM and KFM) and increase impulse. Walking speed has a significant influence on the measurement of external KAM and KFM. Any future difference in knee joint moment should take this influence as a confounding factor.

Knee Joint Moments in Stroke Groups (Differences between Paretic and Non-paretic Legs)

KAM measures (peak and impulse) were not found to be significantly different between the paretic and non-paretic sides in the stroke survivors studied. However, swing time asymmetry ratios were high, with a consistently longer period of non-paretic stance, which would be expected to increase KAM impulse on the non-paretic side. Instead, it is suggested here that the lack of difference in KAM (peak and impulse) between sides is due to the fact that increased pelvic obliquity (tilt) of the paretic limb (see Table 4-1) counteracts the effects of swing time asymmetry. Specifically, increased pelvic obliquity (tilt) reduces the KAM moment arm (Chiba et al., 2016; Linley et al., 2010), and therefore the magnitude of peak KAM on the non-paretic side. KAM that is reduced in magnitude, combined with an increased stance time on the non-paretic side, will serve to maintain KAM impulse, with respect to the opposite effect on the paretic side (shortened stance time and higher KAM moment arm). While previous work by Marrocco (2016) failed to statistically compare paretic and non-paretic sides, seven out of nine stroke survivors in the above study also demonstrated lower peak KAM on the non-paretic side (Marrocco et al., 2016), thus supporting the current study findings. The participants in the present study also demonstrated significant swing time asymmetry, and it has been hypothesised that asymmetrical gait increases the risk of joint degeneration (K. K. Patterson et al., 2008). Despite significant swing time asymmetry in the ***whole group of stroke survivors***, the results of the current study indicate that this does not coincide with asymmetric KAM impulse, which may differentially heighten the risk of developing OA in one limb over the other, following stroke.

In the current study, the KFM of the ***whole group of stroke survivors*** showed no significant difference between the paretic and non-paretic sides. Despite the difference between KFM on the paretic and non-paretic sides being statistically tested in the literature, some previous studies have produced contradictory results for KFM asymmetry, with the paretic side proving to be higher than the non-paretic side (Kim and Eng, 2004). Meanwhile, other studies have reported a higher non-paretic side (Marrocco et al., 2016; Teixeira-Salmela et al., 2001). Such contradictory results between studies with regard to KFM asymmetry may be attributed to a range of differences in the characteristics of these studies and their samples; for example, in walking speed (van den Noort et al., 2013), knee RoM (Creaby et al., 2013), spasticity, and spatial asymmetry (Allen et al., 2011; Lamontagne et al., 2007).

Impact Statements:

Despite many stroke survivors displaying temporal asymmetry, knee joint moments between paretic and non-paretic sides were NOT found to be significantly asymmetrical in this study, possibly because pelvic obliquity (tilt) reduces the KAM moment arm.

Differences in Knee Joint Moments between Stroke Groups and Healthy Controls at Different Walking Speeds

The present study found that for the ***whole group of stroke survivors***, KAM impulse was significantly lower on both the paretic and non-paretic sides, compared to healthy controls walking at comparable slower speeds, and on the paretic side, compared to healthy controls walking at SS speeds (see Figure 4-1). When walking at slow speeds, the healthy controls demonstrated significantly higher magnitudes of KAM impulse than was evident among the stroke survivors.

The above results suggest that the compensatory strategies employed by stroke survivors, such as slow walking speed, low propulsion, due to muscle weakness (Kim and Eng, 2003; Lin et al., 2006) (reflected in peak KAM), and pelvic tilt (reflected in KAM impulse) may serve to protect against joint loading patterns, which are known to be risk factors of OA. While previous studies have indicated high variability of peak KAM and KFM among stroke survivors compared to healthy adults (Marrocco et al., 2016) (with some displaying higher moments on the paretic side and others, on the non-paretic side), only six (25%) of the participants in the current study demonstrated higher peak KAM than healthy subjects walking at a matched speed; while four (16%) displayed higher peak KAM than healthy subjects walking at SS speeds (see Table 4-2). Given the prevalent rehabilitation goal of increasing the walking speed of stroke survivors (Dickstein, 2008), future studies should also examine the effects of increased walking speed on their knee loading patterns.

KFM was found to be significantly ***higher*** on the non-paretic side in the stroke survivors studied here, compared to healthy participants walking at a matched speed (with nine participants exceeding the upper 95% confidence limit of the healthy controls) (see Table 4-4),

(see Figure 4-2). It is subsequently proposed that increased KFM is due to greater RoM of the knee on the non-paretic side (Creaby et al., 2013) (see Table 4-1), together with muscle co-contraction (Balasubramanian et al., 2007; Kim and Eng, 2004; B. Raja et al., 2012), which may be the result of compensatory mechanisms for reduced functioning on the paretic side. These compensatory strategies are common in stroke survivors, providing mechanical stability through the stiffening of joints (Beyaert et al., 2015). However, both increased knee RoM and muscular co-contraction have previously been found to increase contact force at the knee, as well as the potential risk of patellofemoral and tibiofemoral joint pain and degeneration (Farrokhi et al., 2015; B. Raja et al., 2012). Likewise, heightened KFM on the non-paretic side has previously been reported in stroke survivors (Kim and Eng, 2004; Teixeira-Salmela et al., 2001), which researchers (Allen et al., 2011) suggest is due to asymmetrical step lengths (i.e. longer paretic step length, owing to increased compensatory propulsion on the non-paretic side and therefore, flexion). Indeed, the current participants demonstrated high step length asymmetry (with six participants displaying a longer paretic side, as opposed to two with a longer non-paretic side). However, few reported joint pain, despite an average of five years since the onset of stroke (see Table 4-1).

Impact Statements:

Given that slow walking speed increases load, KAM peak and impulse were lower for the stroke survivors than for the healthy controls. Again, low KAM may be a side-effect of compensatory strategies that are employed while walking.

However, KFM on the non-paretic side was found to be higher among the stroke survivors studied, compared to healthy controls, indicating a risk of developing knee pain and joint degeneration.

4.4.2 Knee Joint Moment Differences between Sub-groups of Stroke Survivors (Severe and Less Severe Temporal and Spatial Asymmetries)

To the present author's knowledge, the consequences of ***severe spatiotemporal asymmetry*** on knee joint moments in individuals with stroke have never been investigated before. This is despite the fact that asymmetrical gait in other conditions (unilateral amputation and

unilateral OA) is linked with the risk of developing OA in the unaffected limb. Moreover, some of the gait deviations observed in stroke (for example, temporal gait asymmetry and excessive muscle activity) (K. K. Patterson et al., 2008; B. Raja et al., 2012) could contribute to secondary musculoskeletal complications (such as joint degeneration and pain), due to the cumulative effects of excessive and repetitive loading (Andriacchi et al., 2006). To address this gap, one of the present study's aims was to explore knee joint loading patterns in a group of stroke survivors with severe/less severe temporal and spatial asymmetries, compared to healthy controls walking at SS speeds and 0.8 m/s.

Knee Joint Moment in Asymmetry/Symmetry Sub-groups of Stroke Survivors, Compared to the Whole Cohort of Stroke Survivors

While the ratio of peak KAM asymmetry for the whole group (1.19) was similar to what was reported by Marrocco and colleagues (1.19), the asymmetry ratio for the ***temporal asymmetry*** sub-group was 1.42. Peak KAM for the ***temporal asymmetry*** sub-group followed the pattern displayed by the whole cohort and previous work by Marrocco et al. (2016), with higher peak KAM on the paretic side. However, there was greater asymmetrical peak KAM in the ***temporally asymmetric*** sub-group than in the cohort as a whole. The higher peak asymmetry ratio of the ***severely asymmetrical sub-group*** may be attributed to the increase in paretic-side pelvic obliquity (tilt). The pelvic obliquity angle on the paretic side was 80% higher in this sub-group than in the whole cohort of stroke survivors, thus possibly reducing peak KAM on the non-paretic side. Similarly, pelvic obliquity explains the patterns of observed peak KAM asymmetry in the ***spatial asymmetry*** sub-group of stroke survivors.

The results of both the ***spatial and temporally asymmetric*** sub-groups indicate that the more severe the spatiotemporal asymmetry, the greater the pelvic obliquity (Van Criekinge et al., 2017) and, consequently, peak KAM asymmetry (see Table 4-1 and Figure 4-3). However, the ***temporal symmetry*** sub-group showed higher KAM impulse (not peak) asymmetry (as the KAM impulse on the non-paretic side was higher than on the paretic side), compared to the whole cohort of stroke survivors. In addition to slow walking speed, this asymmetry is most likely due to lower pelvic tilt on the paretic side in this group (-0.08°), compared to the whole cohort of stroke survivors (1.0°) and other sub-groups (0.6-1.8°). This further supports the role of pelvic movement pattern as a potential modifier of knee joint load on the frontal plane

in stroke survivors. Considering the hypothesis that links spatiotemporal asymmetry with the risk of OA on the non-paretic side (Norvell et al., 2005; K. K. Patterson et al., 2008; Patterson and Sibley, 2016), the contribution of pelvic tilt in the present study disproves the above hypothesis by reducing load on this side. Therefore, future work should consider the link between spatiotemporal asymmetry, pelvic obliquity, and the frontal plane of the knee joint moment in stroke survivors.

High knee RoM is linked with high KFM, while knee RoM is higher at faster speeds. Accordingly, the sub-group of participants with the fastest walking speed (the ***temporally symmetrical*** sub-group) had the highest and least asymmetrical KFM. Conversely, the ***temporal asymmetry*** sub-group displayed lower KFM magnitude as higher asymmetry between limbs. The results of the current study for the ***spatial asymmetry*** sub-group are consistent with those published by Allen et al. (2011), who showed that for stroke survivors with longer paretic step length, KFM increases on the non-paretic side (because of foot and knee-muscle propulsion). The above study also indicated that the stroke survivors with symmetrical step length showed no difference in KFM between sides. This supports what has been suggested in earlier studies, namely that stroke survivors with symmetrical step length have equal foot propulsion on the paretic and non-paretic sides and consequently, symmetrical KFM.

Impact Statements:

The more severe the spatiotemporal asymmetry, the greater the pelvic obliquity and peak KAM asymmetry. However, the temporally symmetrical participants showed the greatest asymmetry in their KAM impulse and the greatest KFM (owing to higher speed and knee RoM).

Given that increasing speed and reducing asymmetry are prominent goals for rehabilitation, future work should explore the link between temporal symmetry and asymmetry and walking speed, with regard to joint moments.

Knee Joint Moment in Asymmetry/Symmetry Sub-groups of Stroke Survivors and Healthy Participants Walking at SS Speeds and 0.8 m/s

Gait after stroke is characterised by slow walking speed and spatiotemporal asymmetries. However, little is known about the nature of kinetic asymmetries and the consequences of persistent severe spatiotemporal asymmetry, compared to a healthy control group walking at an equivalent speed. In particular, there is a lack of knowledge relating to abnormal knee joint moments (as opposed to healthy knee joint moments), which may indicate a biomechanical mechanism for the development of comorbid OA.

The SS speeds of the healthy control participants were higher than those of all sub-groups of stroke survivors and as a result, the stroke survivors' peak KAM was ***lower*** than that of the healthy participants. This was inconsistent with a previous study, which demonstrated that there was no difference in KAM between stroke survivors and healthy controls walking at SS speeds (Marrocco et al., 2016). Such conflict between studies is likely to be due to the severe spatiotemporal and kinematic asymmetry and slow walking speed of the current study participants. In contrast, Marrocco et al. (2016) were high functioning and had a high walking speed, with better spatiotemporal symmetry.

The KAM impulse of the healthy controls ***decreased*** with a higher walking speed (by 33.3%), compared to a slow speed (see Figure 1.4) (Robbins and Maly, 2009). Accordingly, the KAM impulse of most of the stroke survivor sub-groups was comparable to that of the healthy controls, walking at SS speeds (where the SS speeds of the healthy subjects were higher than those of the stroke survivors). However, the KAM impulse of the paretic side in the ***temporal symmetry*** sub-group and of both the paretic and non-paretic sides in the ***spatial asymmetry*** sub-group was ***lower*** than in the healthy controls, walking at SS speeds (see Figure 1.5 and 1.6). This reduced KAM impulse in these two sub-groups may be attributed to an increase in pelvic tilt on the non-paretic side (-0.7°) in the ***temporal symmetry*** sub-group, compared to healthy controls (-3.71°); consequently decreasing KAM impulse on the paretic side. This reduction can also be explained by the combination of severe swing time step length asymmetry between sides in the ***spatial asymmetry*** sub-group (see Table 4-1).

At a slow matched speed (0.8 m/s), the peak KAM of the healthy controls was 13% lower than at SS speeds. The peak KAM of most of the stroke survivors in the ***temporal asymmetry*** and

symmetry sub-groups, except on the non-paretic-side in the ***temporal asymmetry*** sub-group***,*** was comparable to that of slow healthy walkers. However, peak KAM on the non-paretic side of the ***temporal asymmetry*** sub-group was lower than that of the healthy controls. This may be due to the increase in pelvic tilt (by 4.5°), compared to healthy controls walking at a slow speed. The peak KAM of most individuals in the ***spatial asymmetry*** and ***symmetry*** sub-groups***,*** except on the paretic side in the ***spatial symmetry sub-group,*** was lower than in the healthy controls walking at 0.8 m/s. Meanwhile, peak KAM on the paretic side in the ***spatial symmetry*** sub-group was comparable to that of the healthy controls. This is most likely due to the higher walking speed of this sup-group, compared to that of the other stroke survivor sub-groups, who showed an overall increase in peak KAM. This may also be due to severe asymmetry in pelvic movement patterns between sides.

While slow walking speed was found to increase KAM impulse by 33.3% in the healthy subjects, in contrast to SS walking speeds (see Figure 1.4), KAM impulse on both sides was lower in all the stroke survivor sub-groups than in the healthy controls, walking at a matched speed. This finding contradicts those of previous studies, which show that KAM impulse increases with slow walking speed (Robbins and Maly, 2009). The above inconsistent finding for stroke survivors' KAM impulse, compared to healthy controls, may be attributed to residual impairments; resulting in a number of biomechanical adjustments to minimise knee joint load while walking, thus reducing speed and GRF (Balasubramanian et al., 2007; Kim and Eng, 2003; Bhavana Raja et al., 2012; Sheffler and Chae, 2015).

In the current study, the KFM of the ***temporal and spatial symmetry*** sub-groups of stroke survivors was comparable to that of healthy controls walking at SS speeds. However, it was higher than in healthy controls walking at a slow matched speed. Increased KFM was most likely due to higher walking speed in the ***symmetrical*** sub-groups (see Table 4-1). In addition, similar foot propulsion and GRF on the paretic and non-paretic sides among the ***symmetrical*** stroke survivors during walking, as proposed by previous studies (Balasubramanian et al., 2007; Kim and Eng, 2004), may reflect increasing KFM, compared to healthy slow walkers. The current study findings are supported by Allen et al. (2011), who showed that KFM (in the pre-swing phase) on the paretic and non-paretic sides of stroke survivors with ***symmetrical*** step length was higher than in healthy controls. Heightened KFM may in fact develop the risk of patellofemoral joint pain and knee joint degeneration (Teng et al., 2015).

In contrast, while the KFM of ***temporal and spatial asymmetry*** sub-groups was comparable to that of healthy controls walking at a slow speed (0.8 m/s), it was lower than in healthy controls walking at SS speeds. This finding is most likely due to reduced walking speed (see Table 4-1) (Ardestani et al., 2016; van den Noort et al., 2013; Zeni and Higginson, 2009) and low forward propulsion (Kim and Eng, 2003; Lin et al., 2006) (reflected in KFM), which may serve to protect against joint loading patterns, in contrast to the other sub-groups.

Impact Statements:

The KAM of stroke survivors with spatiotemporal asymmetry/symmetry did not exceed that of healthy controls walking at SS and slow speeds. This may be explained by the effect of slow walking speed and compensatory pelvic tilt.

The KFM of stroke survivors with temporal and spatial symmetry was higher than that of healthy controls walking at a slow speed. These symmetrical sub-groups may therefore be vulnerable to the development of patellofemoral joint pain and knee joint degeneration.

4.5 Limitations of the Study

One limitation of this study is that physical activity was not assessed, which could have provided important additional insights into the extent to which stroke survivors experience repetitions of high KFM in daily life. A further limitation of this study is the absence of radiographic data for the stroke survivor sub-groups and healthy controls, giving rise to the possibility that there were structural changes associated with the knee joint in the participants. Accordingly, estimating knee joint load and the potential risk of OA depends on external knee joint moments (KAM and KFM), not structural changes in the joint, such as radiographic examination.

The small sample size of the stroke cohort and healthy groups is another limitation of this current study. According to the post-hoc power calculation, the sample size should have consisted of at least 28 healthy subjects and 30 stroke survivors. This lack of difference in KAM and KFM variables between the stroke survivors may relate to this limitation. Considering the clinical relevance of the nature of knee joint moment, the need for further large-sample studies is implied, in order to confirm the change of moment. Moreover, the

relatively small sample size of stroke survivor sub-groups (severe and less severe ***spatiotemporal asymmetry*** sub-groups) could have influenced the differences in knee joint moment.

4.6 Future Work

Future studies should examine joint loading patterns longitudinally in sub-groups of acute stroke, both with and without knee pain. Given that rehabilitation goals often aim to remediate compensatory gait patterns and restore more normative kinematics and kinetics, it is important to understand the nature of knee joint moments with increased walking speed and symmetry.

Using an inverse dynamic approach to estimate intersegmental force does not provide a clear insight into the force of knee joint contact. Since measuring contact force *in vivo* is extremely difficult, musculoskeletal modelling may be considered as an alternative approach to estimating knee joint contact force, due to the contribution of individual muscles during walking. Conducting such work as future research would enable further analysis of the magnitude of contact force on stroke survivors' knee joints, particularly on the non-paretic side.

Finally, the link between stroke survivors' compensatory mechanisms and biomechanical changes during walking (such as pelvic obliquity, trunk lean, knee joint RoM, and foot propulsion) and altered knee joint moments should be studied.

4.7 Conclusions

This would appear to be the first study to characterise the knee joint moments of chronic stroke survivors (in general, and based on spatial and temporal asymmetries). As such, this work provides important indications for future research and potential targets for gait rehabilitation, in order to reduce the longer-term risk of stroke survivors developing knee OA. While all frontal plane moments were found to be comparable to/lower than those of healthy subjects walking at comparable speeds, there was asymmetry in knee joint loads between the paretic and non-paretic sides on the frontal plane, and high knee joint load on the sagittal plane in most of the stroke sub-groups. This pattern of moments may leave stroke survivors

vulnerable to the development of patellofemoral joint pain and knee joint degeneration. Stroke-related biomechanical changes to walking patterns (either with severe or less severe spatiotemporal asymmetries), such as changes in walking speed (which are rehabilitation targets) and knee RoM, may contribute to heightened KFM, but pelvic tilt could also offer protection against KAM patterns that are predictive of OA. Rehabilitation efforts should therefore consider the effects of these compensatory walking patterns over stroke survivors' recovery time. Future longitudinal work is needed to investigate knee joint loads from the early stages of stroke recovery, considering cumulative load (physical activity), walking speed, and radiographic measures of joint tissue.

Chapter 5: The Influence of Imposing Spatiotemporal Symmetry/Asymmetry on Knee Joint Kinetic Profiles in in Individuals with Stroke.

This chapter aims to explore the immediate effect of imposing spatially and temporally symmetrical and asymmetrical gait patterns on knee joint moment profiles in stroke survivors.

5.1 Background

Recovering basic locomotor functions after stroke is one of the most important challenges facing stroke survivors. Despite the majority of stroke survivors being able to walk unaided after an extensive rehabilitation process (Balaban and Tok, 2014), numerous impairments may remain, including slow speed and alterations in kinematic and kinetic parameters (Beyaert et al., 2015; Lamontagne et al., 2007; Wonsetler and Bowden, 2017a). In particular, hemiplegic gait is characterised by asymmetric gait parameters between limbs, due to the cross-hemispheric organisation of motor networks (Wonsetler & Bowden, 2017). Severe gait asymmetry may be caused by stroke-related neurological deficits (i.e. loss of leg strength, impaired balance, muscle co-contraction, and spasticity); all of which may limit forward progression during walking and thereby reduce independence (Hendrickson et al., 2014). Therefore, it has been hypothesised that gait asymmetry may be connected to many potential deleterious side effects, such as challenges to balance control (increased risk of falls), increased energy expenditure, increased risk of musculoskeletal injury to the non-paretic lower extremity, and reduced overall activity (Balaban and Tok, 2014; Kim et al., 2016; Li et al., 2018; Patterson and Sibley, 2016). Accordingly, a wide range of treatment approaches and interventions have been developed to improve post-stroke gait patterns and consequently, quality of life for stroke survivors (Beyaert et al., 2015; Langhorne et al., 2009; Winstein et al., 2016).

Treatment that targets gait symmetry in stroke survivors (i.e. to reduce asymmetry) is very important, because it improves features of a person's walking (the patient's priorities for recovering the aesthetics of gait, or 'normal'-looking walking (Winstein et al., 2016)), and the participation of those who have suffered a stroke (by improving metabolic and mechanical efficiency (Beyaert et al., 2015)). However, the fact of whether rectifying (or failing to rectify) asymmetry helps avoid the potentially negative consequences of joint

degeneration/musculoskeletal injury, **assumed** to result from an asymmetrical walking pattern (K. K. Patterson et al., 2008; Patterson and Sibley, 2016), is not known. Numerous studies have evaluated interventions aimed at restoring walking symmetry in stroke survivors, using various treatment modalities, such as muscle-strengthening exercises and physical conditioning (Teixeira-Salmela et al., 2001), rhythmic auditory stimulation/external auditory cues (Hollands et al., 2016; Wright et al., 2013), and a split-belt treadmill (Helm and Reisman, 2015; Lewek et al., 2018; Malone and Bastian, 2014; D. S. Reisman et al., 2013). Nevertheless, despite these studies showing improved spatiotemporal symmetry and walking speed, no study has investigated the impact of imposing gait symmetry on the joint kinetic profiles of stroke survivors' lower limbs (see Search Strategy, Appendix A.7).

Given the many reasons for expecting post-stroke spatiotemporal asymmetry to alter knee joint moments, the aim of this study was to explore the immediate effect of imposing spatially and temporally symmetrical and asymmetrical gait patterns on knee joint moment profiles (as an established reflection of joint loading) in stroke survivors. In order to accomplish this, the present research set out to:

- Measure the immediate effect of altering temporal gait asymmetry (by imposing swing time symmetry) on stroke survivors' knee moment profiles during walking.
- Measure the immediate effect of altering spatial gait symmetry (by imposing step length symmetry) on stroke survivors' knee moment profiles during walking.
- Measure the immediate effect of altering temporal gait symmetry (by imposing swing time asymmetry) on stroke survivors' knee moment profiles.
- Measure the immediate effect of altering spatial gait symmetry (by imposing step length asymmetry) on stroke survivors' knee moment profiles.

5.2 Methods

5.2.1 Participants

A sample of adult (>18yrs) community-dwelling stroke survivors, both male and female, were recruited from previous studies and community support groups in Greater Manchester, UK, and King Fahad Medical City (KFMC), Saudi Arabia.

A group of healthy adults (>18yrs), recruited from the University of Salford's staff, previous studies at the University of Salford, and the CitizenScientist website, also participated in a control group for this research. The inclusion and exclusion criteria applied were similar to those used for the previous study, reported in Chapter 3, section 3.1, but with additional exclusion criteria for the healthy participants, as set out below:

Exclusion criteria (healthy participants):

- Healthy participants with a swing time asymmetry ratio >1.06 and step length asymmetry ratio >1.08 were excluded (these being the suggested thresholds for 'abnormal' symmetry, based on the upper 95% CI of spatial and temporal asymmetry ratios in a healthy population (Patterson et al., 2010)).

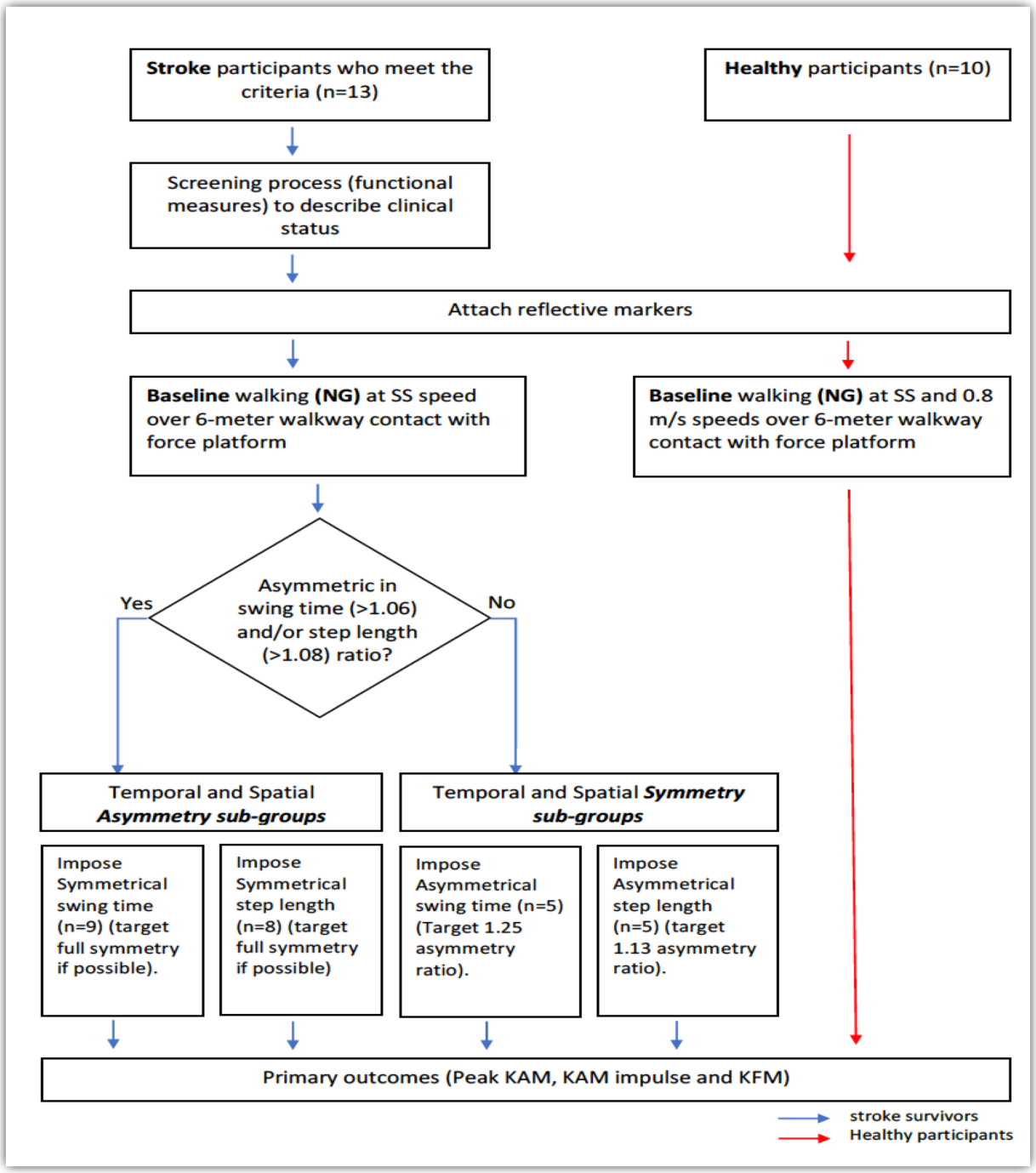


Figure 5-1: Study procedure flow chart.

5.2.2 Procedure

The procedures were similar to those adopted in the previous study (see Chapter 3, section 3.3). For example, the participants were fitted with single-reflective passive markers and cluster markers, using the CAST marker model. They then walked along a six-metre walkway for a minimum of five trials. Kinetic data were obtained from embedded force plates, and kinematic data were collected using a motion capture system. The metronome software,

MatTAP (MATLAB Timing Analysis Package) was used as an additional tool to help impose symmetrical and asymmetrical gait patterns onto the participants (Elliott et al., 2009). This highly accurate metronome generates up to two independent tones/beats and allows users to adjust numerous features, such as interval frequency, tone duration, and frequency, as well as the length of the synchronisation period. Importantly, it also offers the option of individualising metronome intervals and phase shifts. A dual-tone metronome is recommended, since, compared to a single-tone metronome, it provides cueing for each step, thus enabling stronger auditory-motor synchronisation (i.e. more control over beats in relation to each other, in order to impose symmetry/asymmetry) (Roerdink et al., 2009; Wright et al., 2013) (see Figure 5-2). In addition, a stepping-to-footprint function imposed step length asymmetry.

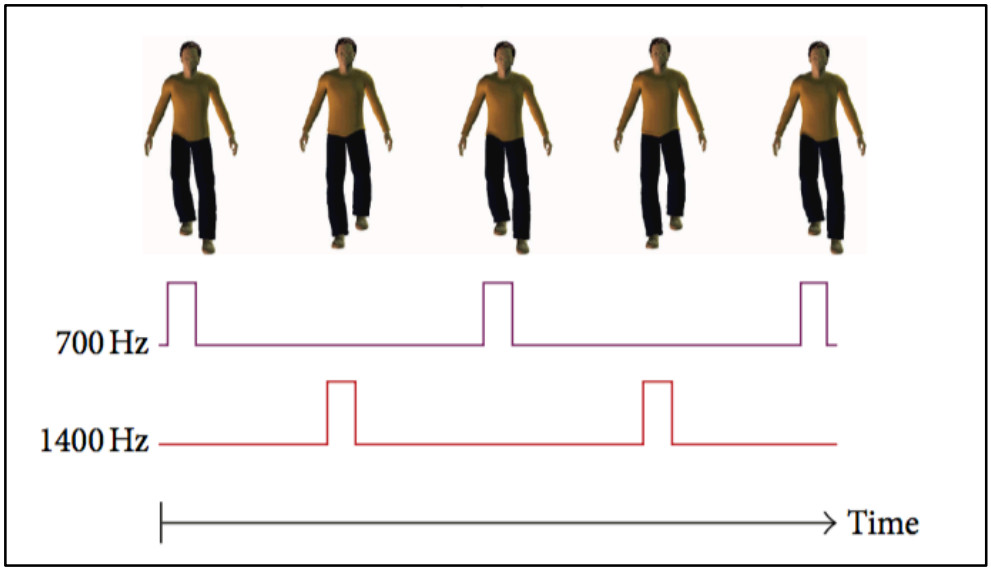


Figure 5-2: Auditory-cued stepping by using dual-tone metronome (Wright et al., 2013).

5.2.3 Data collection

Each of the stroke participants walked along the six-metre walkway with embedded force platforms, under the three following conditions: 1) Self-selected (SS) walking pattern (baseline), 2) Temporal (a)symmetry, and 3) Spatial (a)symmetry. This is explained in greater detail below:

Natural Gait (NG) (baseline data): all the participants walked at their natural SS speed and degree of (a)symmetry, for at least five times in total (see Figure 5-3a), following all the instructions given in section 3.4. In addition to their SS speed, the healthy participants walked at a slower speed (0.8 m/s), which corresponded to the mean walking speed of the stroke survivors. The values for the spatiotemporal parameters (i.e. swing time, step length, and stride time [cycle time]), recorded under these baseline walking conditions, were used as inputs for imposing temporal and spatial symmetry and asymmetry.

- **Imposing symmetry for stroke survivors with asymmetrical gait:**
    - **Temporal (a) symmetry:**

- The stroke survivors with ***temporally asymmetrical*** gait at NG/baseline (***swing time ratio >1.06***) were asked to walk while stepping in synchronisation with an external auditory cue (i.e. a dual-tone metronome) (Pelton et al., 2010; Wright et al., 2013). The auditory cue was a time reference, with which the participants could synchronise their foot contact, such that the time spent in swing and stance was equal for both legs (i.e. the time between the metronome pulses was identical and coincided with the mean duration of swing on the average of both sides under NG/baseline conditions (Wright et al., 2013)). The starting point for the walking trials was adjusted so that the stroke survivors were guaranteed to hit the force platform in the middle, without having to aim for it themselves.

- The stroke survivors with ***temporally symmetrical*** gait under NG/baseline conditions (***swing time ratio <1.06***) were asked to walk, stepping in synchronisation with an external auditory cue (as mentioned above). However, in this case, the auditory cue was a time reference, with which the participants could synchronise their foot contact, such that the time spent in swing and stance was equal to the asymmetrical cut-off ratio of 1.25 (the normative stroke, swing time ratio (Patterson et al., 2010)), in order to impose temporal asymmetry (see Figure 5-3c).

    - **Spatial (a) symmetry:**

    The stroke survivors with ***spatially asymmetrical*** gait at NG/baseline (***step length ratio >1.08***) were asked to step to a step target cue while walking (see Figure 5-3b).

The step target cue was a step length reference, with which the participants could synchronise their foot contact, such that the step length distance was equal for both legs (based on the average step length on both sides under NG/baseline conditions). The starting point for the walking trials was adjusted in a way that guaranteed the survivors hitting the force platform in the middle, without having to aim for it themselves.

The stroke survivors with ***spatially symmetrical*** gait at NG/baseline (***step length ratio <1.08***) were asked to step to a step target cue while walking (as mentioned above). However, in this case, the step target cue was a step length reference, with which the participants could synchronise their foot contact, such that the step length distance was equal to the asymmetry cut-off ratio of 1.13 (the normative stroke step length asymmetry ratio (Patterson et al., 2010)), in order to impose spatial asymmetry (see Figure 5-3b).

Baseline (natural) walking was completed first in each case and then the other two conditions (temporal and spatial) were imposed in a randomised order. Trials for all conditions and all groups were deemed successful for analysis, if the force platform captured at least one stance phase (i.e. the foot landed entirely on the force platform), and the walking speed for all walking trials was within the average calculated for the stroke participants (based on NG walking speeds).

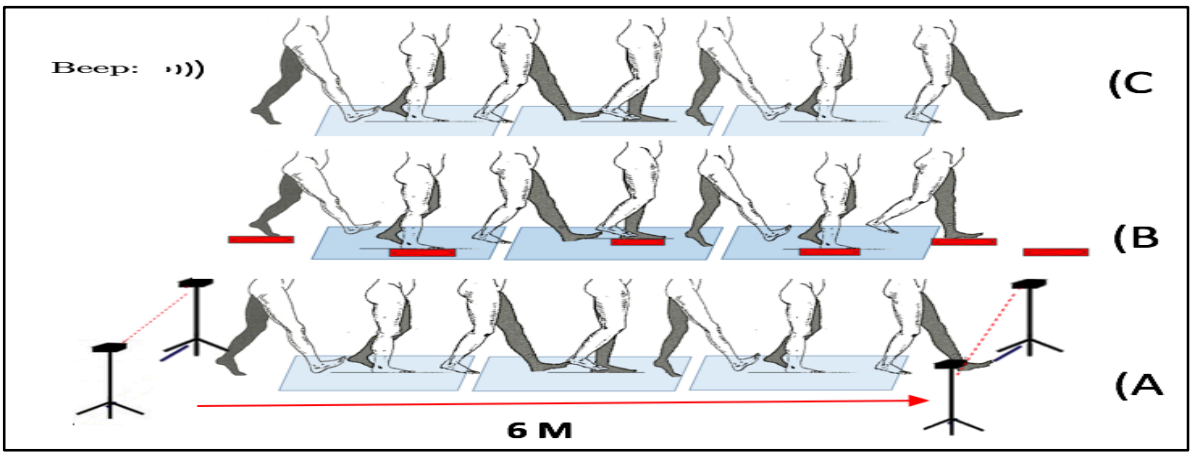


Figure 5-3*:* Walking conditions: A) NG/Baseline – typical gait, set to a metronome over force platforms embedded in the floor (blue squares); B) Spatial, (i) symmetry – imposing step length symmetry/asymmetry by stepping onto footprint targets; C) Temporal, (i) symmetry – imposing swing time symmetry/asymmetry via a metronome. Walking speed was monitored by timing gates at either end of the six-metre walkway

5.2.4 Data processing

In short, the data-processing consisted of labelling the trial markers, using 3D motion analysis software to define the body segments, according to the correct anatomical landmarks. Next, all the dynamic trials were saved (in C3D format) and exported to Visual3D software. Five successful walking trials (under each condition), with force-plate data from one full stance phase on each limb for each participant, were used for analysis. Spatiotemporal, kinematic, and kinetic data were processed using Visual3D. Further enhanced details are presented in Chapter 3, section 3.5.

5.2.5 Statistical analysis

Descriptive measures (mean ± standard deviation [SD] and 95% confidence intervals [CI]) of the participants' characteristics were used to summarise demographic details for all sub-groups.

The purpose of this study was to define the change in joint moment after imposing spatiotemporal symmetry/asymmetry, following a stroke. Accordingly, the recruited group of stroke survivors (n=13) was split unevenly into small sub-groups, based on the baseline spatiotemporal asymmetry/symmetry of swing time and step length ratios, which were reported in the previous study (Patterson et al., 2010). Consequently, this limits statistical power, and full statistical analysis is unsuitable for detecting changes between sub-groups.

A comparison between the mean of each sub-group, against the 95% CI values, and the mean values of the healthy controls - walking at different speeds - was used to determine whether the joint moments were 'significantly different' between the two main groups (the stroke survivors and the healthy controls). Specifically, joint loads would be considered 'high', if the mean exceeded the upper limit of the healthy participants' 95% CI; 'low', if the mean fell below the lower limit of the healthy participants' 95% CI, and 'comparable', if the mean fell between the lower and upper limits of the healthy participants' 95% CI. ES, using the Cohen's *d* method (Cohen, 1992), were then calculated (with G*Power Version 3.1.1, Universität Kiel, Germany). The corresponding 95% CI of ES was also provided by using the following formula (Lee, 2016):

$$\sigma(d) = \sqrt{\frac{N_1+N_2}{N_1 \times N_2} + \frac{d^2}{2(N_1+N_2)}}$$

$$95\%\ \text{CI for Cohen's } d\text{: } [d - 1.96 \times \sigma(d),\ d + 1.96 \times \sigma(d)]$$

(N: The sample size of group 1 and 2)

5.3 Results

5.3.1 Participants

Thirteen stroke survivors (Salford n=11, Saudi n=2) were included, with a mean age of 60.3 (SD 13.5) years and post-stroke period of 6.9 (SD 12.1) years. These stroke survivors were classified into different sub-groups based on the baseline spatiotemporal asymmetry/symmetry of their swing time and step length ratios: the ***asymmetry temporal*** (n=9), ***symmetrical temporal*** (n=4), ***asymmetry spatial*** (n=5) and ***symmetry spatial*** sub-groups (n=8).

Three out of the eight participants in the ***spatial symmetry*** sub-group were considered separately (see supplementary data in Appendix B.4). This is because, after imposing step length asymmetry, they did not exceed the target step length asymmetry ratio of 1.08 (the upper limit of the step length symmetry ratio in the healthy controls). Meanwhile, ten healthy adult participants (all from Salford), with a mean age of 54.3 (SD 4.50) years, participated in the study. There were no significant differences found between the left and right legs in any

measure of KAM or KFM (see Appendix A.4). The mean for both legs was therefore used in a statistical comparison with the stroke survivors.

Clinical and demographic descriptors of all participants are summarised in Table 5-1.

Table 5-1: Participants' demographics – continuous variables are presented as means (SD), while nominal variables are presented as numbers. Mean values of gait parameters (in both limbs) are provided for SS and 0.8 m/s walking speeds amongst the healthy controls. Swing time and step length symmetry ratios are calculated as the ratio between the two legs (maximum/minimum). Positive values of pelvic obliquity indicate frontal hike of the ASIS marker on the swing side. (∗) Three out of eight stroke participants did not achieve the target step length asymmetry and are reported in Appendix B.4.

Groups	Stroke survivors					Healthy Control	
	Whole group	Sub-groups					
		Temporal		Spatial		SS	0.8 m/s
		Asym >1.06	Sym <1.06	Asym >1.08	Sym <1.08		
N	13	9	4	5	5/8*	10	
Age (years)	60 (13.5)	62.9(13.2)	50.5(14.0)	61.4(14.9)	65.6(10.9)	54.3(4.9)	
Sex							
Male	10	7	3	3	4	10	
Mass (Kg)	74.2(10.1)	71.0(9.2)	81.3(9.8)	68.6(11.6)	80.0(9.1)	83.8(10.8)	
Height (m)	1.7(0.1)	1.7(0.1)	1.7(0.1)	1.7(0.2)	1.7(0.1)	1.7(0.1)	
BMI (Kg/m^2)	25.5(3.1)	24.8(2.6)	27.1(3.8)	25.1(3.6)	26.8(3.0)	28.3(3.2)	
TUG (S)	15.2 (5.3)	17.5(4.8)	10.1(1.15)	17.1(5.9)	13.1(5.3)	n/a	
Time since stroke (years)	6.9 (12.1)	3.9(2.1)	13.7(22.1)	3.02(0.93)	13.5(18.7)	n/a	
BBS	50.8 (5.4)	49.2(5.9)	54.3(1.3)	48.6(7.6)	53.2(2.3)	n/a	
Fugl-Meyer lower limb	26.7 (4.6)	25.2(5.2)	30.0(5.7)	24.8(4.9)	29.4(5.9)	n/a	
KOOS Pain subscale	99.2(3.1)	100.0(0.0)	97.2(5.6)	100.0(0.0)	97.8(4.97)	n/a	
Affected side							
Left side	7	4	1	2	2	n/a	
Right side	6	5	3	3	3	n/a	
Walking speed (SS) (m/s)	0.85 (0.3)	0.72(0.2)	1.16 (0.09)	0.70(0.3)	1.04(0.18)	1.28(0.2)	0.9 (0.14)
Swing time symmetry (ratio)	1.33 (0.26)	1.44(0.2)	1.04(0.01)	1.42(0.16)	1.18(0.14)	1.04 (0.01)	1.02(0.01)
Step length symmetry (ratio)	1.11 (0.1)	1.13(0.10)	1.04 (0.02)	1.21(0.06)	1.05(0.03)	1.04 (0.03)	1.06(0.07)
Pelvic obliquity angle (at time of peak KAM) (°)						-3.71(2.51)	-2.66(2.80)
Paretic	1.0(4.9)	2.64(5.03)	-2.7(1.9)	3.5(4.8)	-0.62(4.9)		
Non-paretic	-2.2(3.96)	-2.60 (4.4)	-1.3 (3.2)	-5.1(3.3)	-1.9(1.96)		
Knee flexion angle (°)						45.54(5.67)	45.00(6.52)
Paretic	31.9(12.2)	27.6(12.3)	41.5(3.2)	28.4(14.8)	34.0(9.2)		
Non-paretic	47.96(9.14)	48.3 (9.0)	47.1(10.7)	53.7(7.0)	45.3(10.2)		
Toe-out angle (°)						15.47(5.83)	14.68(6.77)
Paretic	12.98 (13.9)	13.5(15.6)	11.9(11.1)	17.3(9.3)	14.4(10.1)		
Non-paretic	12.6(8.3)	12.6(7.6)	12.5 (11.0)	11.9(7.7)	16.9(7.8)		

5.3.2 Imposing Swing time and Step length Symmetry on Stroke Survivors Who Are Asymmetrical at Baseline

5.3.2.1 Spatiotemporal Parameters of Imposed Swing time and Step Length Symmetry

The spatiotemporal parameters observed after imposing swing time and step length symmetry ratios on the stroke survivor sub-groups with asymmetrical gait at baseline are presented in Table 5-2. When walking to the metronome, the swing time ratio of the ***temporal asymmetry*** sub-group was reduced by 16%. The participants with baseline temporal asymmetry were able to maintain the SS walking speeds observed at baseline, while walking with temporal symmetry.

In contrast, the step length ratio of the ***spatial asymmetry*** sub-group was reduced by 7.4% when walking to foot-fall location targets. Imposing step length symmetry on the ***spatial asymmetry*** sub-group also caused the participants to reduce their walking speed by 14.3%.

In the ***temporal*** and ***spatial asymmetry*** sub-groups, pelvic obliquity did not change from the observed baseline on either the paretic or non-paretic limb, while walking with imposed symmetry. However, the pelvic obliquity detected was greater than in the healthy controls. In contrast, knee flexion angles were altered from the baseline, during walking under imposed spatial or temporal symmetry. However, the knee flexion angle on the paretic side was remarkably lower than on the non-paretic side and in the healthy controls. Nevertheless, the toe-out angle was slightly reduced after imposing temporal and spatial symmetry, and the toe-out angle on the non-paretic side in the ***spatial asymmetry*** sub-group was lower than in the healthy controls (see Table 5-2).

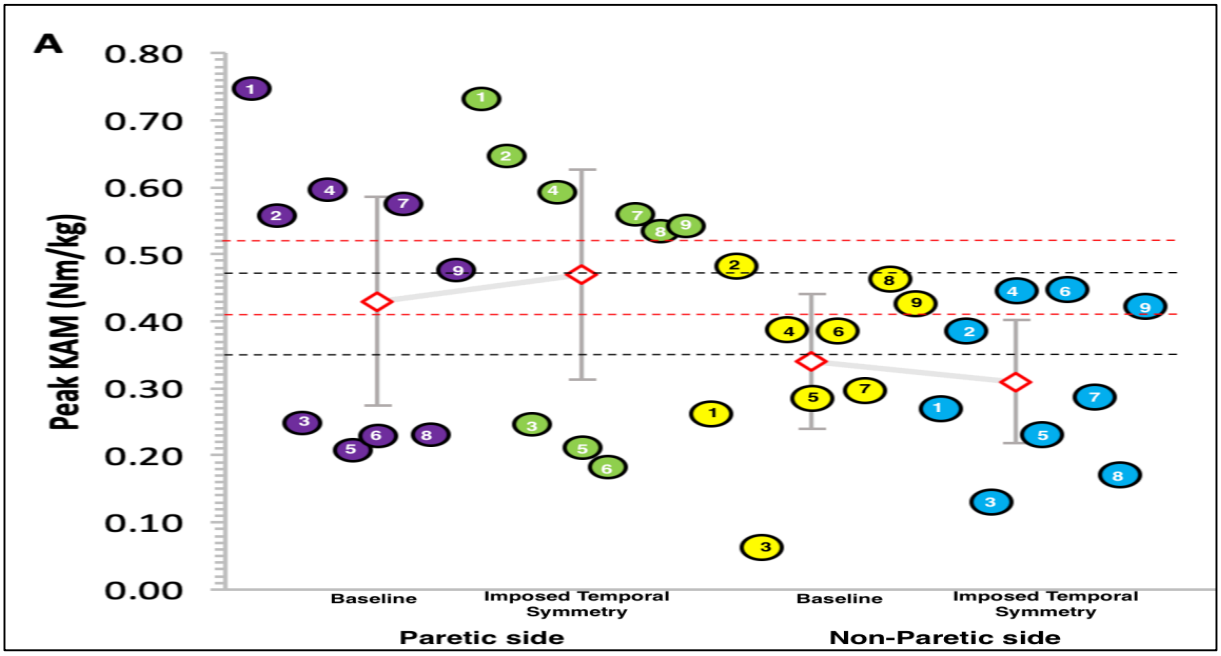
Table 5-2: Mean (SD) gait data for the stroke survivor sub-groups at baseline (asymmetrical condition) and after imposing swing time and step length symmetry. Negative pelvic obliquity values indicated frontal drop in the ASIS marker on the swing side, with respect to the horizontal plane. The text highlighted in red refers to the variables imposed under each condition (SS) Self-Selected walking speed. (ES) Effect Size.

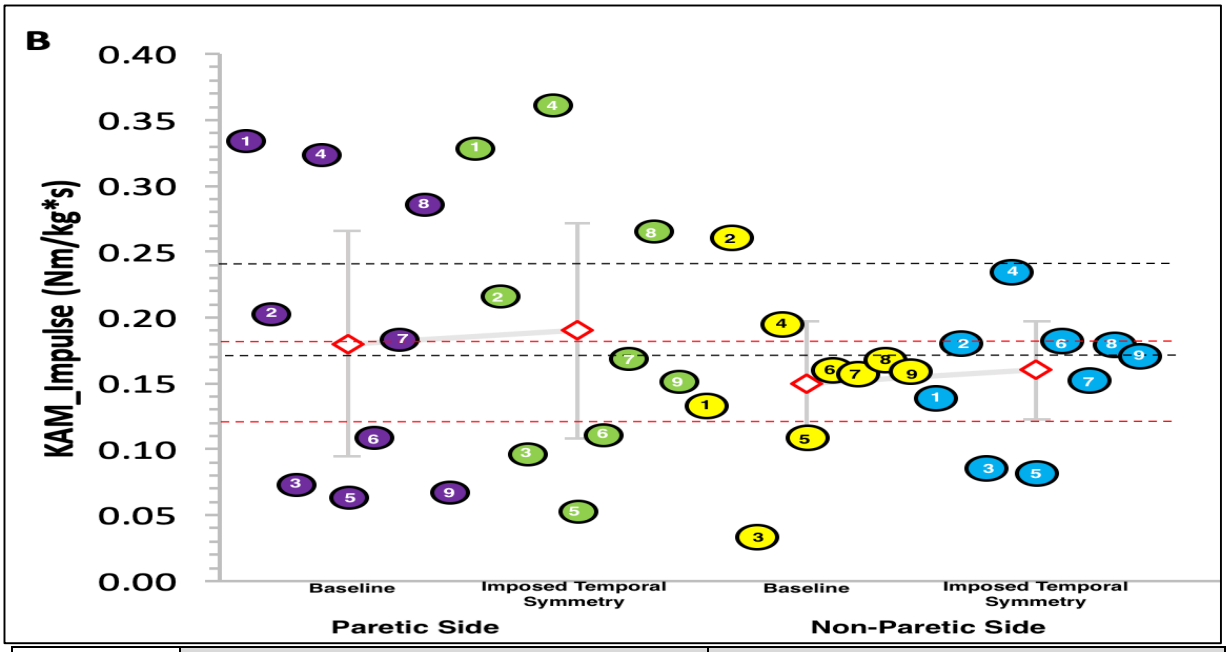
	Temporal Asymmetry (n=9)			Spatial Asymmetry (n=5)			Healthy control (n=13)	
	Baseline	Induced symmetry	ES (95%CI)	Baseline	Induced symmetry	ES (95%CI)	SS	0.8 m/s
Walking speed (m/s)	0.72(0.22)	0.69(0.21)	0.14(-0.79-1.07)	0.70(0.27)	0.60(0.24)	0.39(-0.86-1.64)	1.28(0.2)	0.9 (0.14)
Symmetry ratio								
Swing time	1.44(0.24)	1.21(0.21)	1.44(0.40-2.48)	1.42(0.16)	1.27(0.20)	0.83(-0.46-2.12)	1.04 (0.01)	1.02(0.01)
Step length	1.13(0.10)	1.11(0.09)	0.21(-0.72-1.14)	1.21(0.06)	1.12(0.04)	1.77(0.31-3.23)	1.04 (0.03)	1.06(0.07)
Pelvic obliquity angle (at time of peak KAM) (°)								
Paretic	2.64(5.03)	2.72(5.56)	0.02(-0.90-0.94)	3.52(4.77)	3.59(3.89)	0.02(-1.22-1.26)	-3.71(2.51)	-2.662(2.80)
Non-Paretic	-2.60(4.37)	-2.47(4.91)	0.03(-0.89-0.95)	-5.05(3.25)	-4.94(4.05)	0.03(-1.21-1.27)		
Knee flexion angle (°)							45.54(5.67)	45.00(6.52)
Paretic	27.57(12.28)	32.08(13.63)	0.35(-0.58-1.28)	28.44(14.78)	31.35(14.05)	0.20(-1.04-1.04)		
Non-Paretic	48.34(9.04)	41.62(9.03)	0.74(-0.22-1.70)	53.72(7.02)	52.46(5.45)	0.20(-1.04-1.04)		
Toe-out angle (°)							15.47(5.83)	14.68(6.77)
Paretic	13.48(15.62)	11.88(17.88)	0.10(-0.82-1.02)	17.27(9.32)	14.05(11.47)	0.31(-0.94-1.56)		
Non-Paretic	12.63(7.60)	12.89(7.36)	0.03(-0.89-0.95)	11.93 (7.68)	8.51(7.99)	0.44(-0.81-1.69)		

5.3.2.2 KAM after Imposing Swing Time Symmetry on the Temporally Asymmetric Sub-group

At baseline, paretic peak KAM in the ***temporal asymmetry*** sub-group was comparable to that of the healthy controls, walking at SS speeds and 0.8 m/s, but peak KAM on the non-paretic side was below the lower limit of the healthy controls' 95% CI, walking at SS speeds and 0.8 m/s (see Figure 5-4a). The imposition of swing time symmetry caused a marginal increase in peak KAM on the paretic side, compared to the stroke survivors' baseline, but on the non-paretic side, peak KAM was slightly reduced. However, the slight increase in peak KAM on the paretic side and the slight decrease in peak KAM on the non-paretic side, after imposing swing time symmetry, caused an overall increase in the asymmetry of peak KAM (20%), between the paretic and non-paretic sides compared to baseline conditions. After imposing swing time symmetry, two more stroke survivors (22.2% of the participants, in addition to 5 participants at baseline) showed an increase in peak KAM on the paretic side, which exceeded the upper limit of the heathy controls' 95% CI, walking (symmetrically) at either SS speeds or 0.8 m/s (see Figure 5-4a).

The baseline KAM impulse on the paretic side in the ***temporal asymmetry*** sub-group was comparable to that of the healthy controls, walking at SS speeds and 0.8 m/s. In contrast, while the KAM impulse at baseline on the non-paretic side was comparable to that of the healthy controls, walking at SS speeds, and compared to the healthy controls, walking at 0.8m/s, the KAM impulse on the non-paretic side was below the lower limit of the healthy controls' 95% CI. Imposing swing time symmetry did not cause any appreciable changes in KAM impulse on either the paretic or non-paretic sides, compared to baseline conditions (see Figure 5-4b).





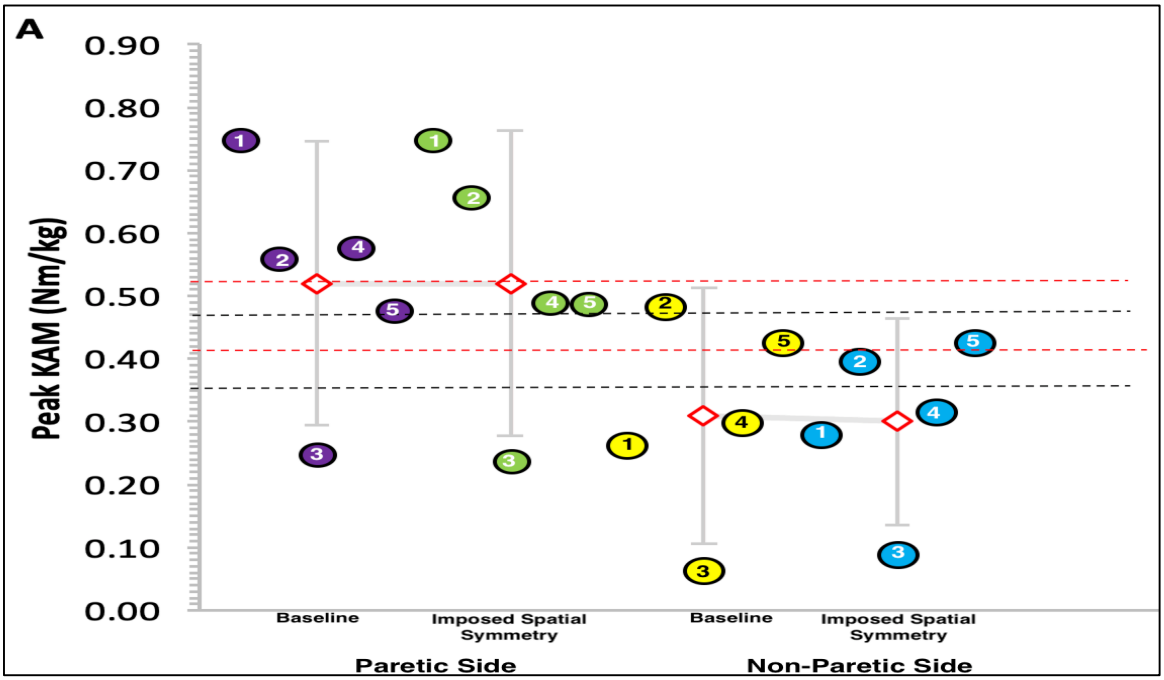
	Paretic side			Non-paretic side		
	Baseline	Imposed Temporal Sym.	ES (95% CI)	Baseline	Imposed Temporal Sym.	ES (95% CI)
Peak KAM	0.43(0.20)	0.47(0.20)	0.20(-0.73-1.13)	0.34(0.13)	0.31(0.12)	0.24(-0.69-1.17)
KAM Impulse	0.18(0.11)	0.19(0.11)	0.10(-0.82-1.02)	0.15(0.06)	0.17(0.05)	0.36(-0.57-1.29)

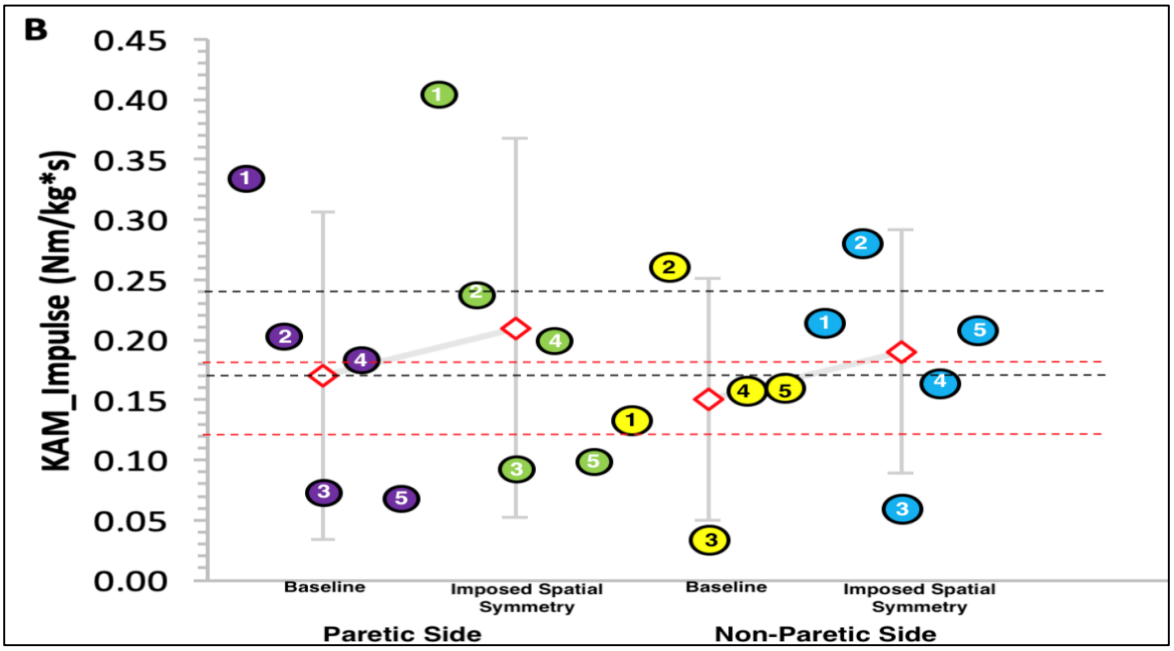
Figure 5-4: Mean knee joint moments (peak KAM and Impulse) in the stroke survivors (red diamonds) and 95% CI, indicated by whiskers at baseline and after imposing temporal symmetry – individual means for each stroke survivor are represented by individual circles for the paretic ([P], purple and green) and non-paretic ([NP], yellow and blue) sides, for A) Peak KAM, and B) KAM impulse. Horizontal dashed lines represent the observed upper and lower 95% CI of the healthy controls (n=10), walking at SS speeds (red) and 0.8 m/s (black). The table presents the observed overall mean (SD) and effect size (ES) of KAM and KAM impulse of stroke survivors' (Baseline and after imposing temporal symmetry) paretic and non-paretic sides.

5.3.2.3 KAM after Imposing Step Length Symmetry on the Spatially Asymmetrical Sub-group

At baseline, peak KAM on the paretic side in the ***spatial asymmetry*** sub-group was comparable to that of the healthy controls, walking at SS speeds, but was higher than that of the healthy controls, walking at 0.8 m/s. In contrast, peak KAM on the non-paretic side at baseline was below the lower limit of the healthy controls' 95% CI, walking at SS speeds and 0.8 m/s. Imposing step length symmetry did not change the magnitude of peak KAM on either side (paretic or non-paretic), nor the asymmetry between sides, compared to baseline conditions (see Figure 5-5a).

The baseline KAM impulse on the paretic side of the ***spatial asymmetry*** sub-group was comparable to that of the healthy controls, walking at SS speeds and 0.8 m/s. In contrast, while KAM impulse on the non-paretic side was comparable to that of the healthy controls, walking at SS speeds, it was below the lower limit of the healthy controls' 95% CI, walking at 0.8 m/s. The imposition of step length symmetry was found to increase KAM impulse on both the paretic and non-paretic sides by 24% and 27%, respectively, compared to baseline conditions. However, this increase in KAM impulse on both sides maintained the KAM impulse asymmetry ratio between the paretic and non-paretic sides at 1.10, corresponding to the baseline conditions. After imposing step length symmetry, KAM impulse on both sides exceeded the upper limit of the healthy controls' 95% CI by 16% on the paretic side and 5% on the non-paretic side, while walking at SS speeds (see Figure 5-5b).





	Paretic side			Non-paretic side		
	Baseline	Imposed Spatial Sym.	ES (95% CI)	Baseline	Imposed Spatial Sym.	ES (95% CI)
Peak KAM	0.52(0.18)	0.52(0.18)	0.00(-1.24-1.24)	0.31(0.16)	0.30(0.13)	0.07(-1.17-1.31)
KAM Impulse	0.17(0.11)	0.21(0.13)	0.33(-0.92-1.58)	0.15(0.08)	0.19(0.08)	0.50(-0.76-1.76)

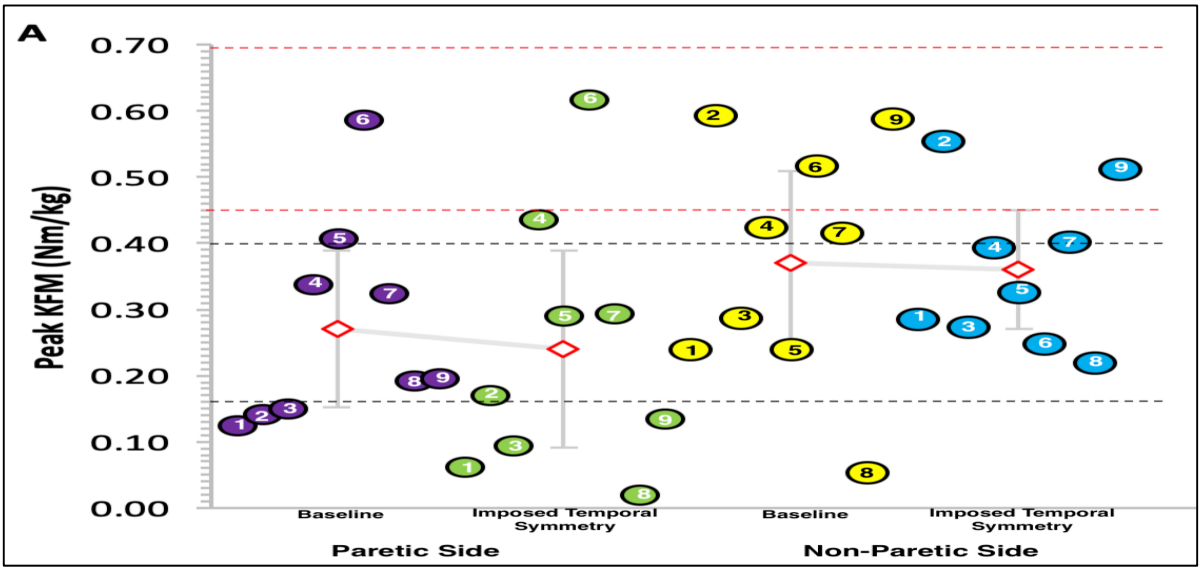
Figure 5-5: Mean knee joint moments (peak KAM and KAM impulse) for stroke survivors (red diamonds) and 95% confidence intervals by whiskers at baseline and after imposing spatial symmetry. Individual means for each stroke survivor are represented by individual circles for the paretic side (P) (purple and green) and non-paretic side (NP) (yellow and blue) for A) Peak KAM and B) KAM Impulse. Horizontal dashed lines represent the observed upper and lower 95% confidence intervals limits of healthy control participants (n=18) walking at SS (red) and 0.8 m/s (black) speeds. The table presents the observed overall mean (SD) and effect size (ES) of KAM and KAM impulse of stroke survivors' (Baseline and after imposing spatial symmetry) paretic and non-paretic sides.

5.3.2.4 KFM after Imposing Swing Time Symmetry on the Temporally Asymmetrical Sub-group

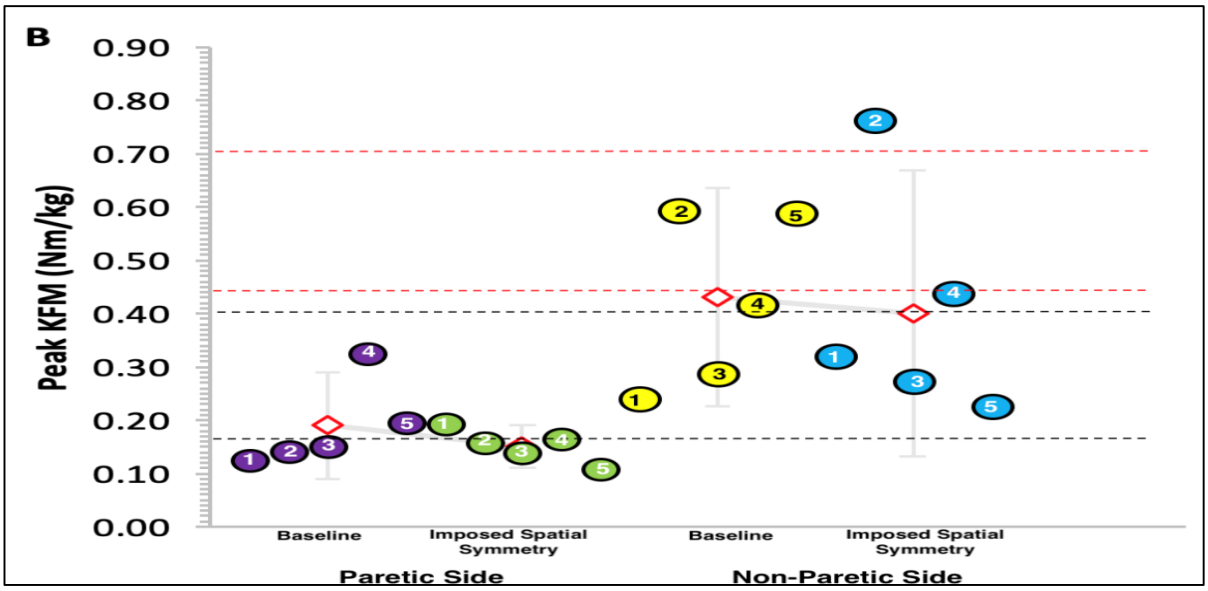
At baseline, peak KFM on the paretic and non-paretic sides in the *temporal asymmetry* sub-group was comparable to that of the healthy controls, walking at 0.8 m/s, but below the lower limit of the healthy controls' 95% CI, while walking at SS speeds. Imposing swing time symmetry slightly reduced peak KFM on both sides (more so on the paretic side), causing a slight increase (9%) in the peak KFM asymmetry ratio between the paretic and non-paretic sides, compared to baseline conditions (see Figure 5-6a).

5.3.2.5 KFM after Imposing Step Length Symmetry on the Spatially Asymmetrical Sub-group

Baseline peak KFM on the paretic side in the ***spatial asymmetry*** sub-group was comparable to that of the healthy controls, walking at 0.8 m/s, but below the lower limit of the healthy controls' 95% CI, walking at SS speeds. In contrast, peak KFM on the non-paretic side was higher than the upper limit of the healthy controls' 95% CI at a walking speed of 0.8 m/s, and below the lower limit of the healthy controls' 95% CI, while walking at SS speeds. The imposition of step length symmetry marginally decreased peak KFM on both sides (more so on the paretic side), causing an increase of 26% in peak KFM asymmetry between the paretic and non-paretic sides, compared to asymmetry under the baseline conditions (see Figure 5-6b).



	Paretic side			Non-paretic side		
	Baseline	Imposed Temporal Sym.	ES (95% CI)	Baseline	Imposed Temporal Sym.	ES (95% CI)
KFM	0.27(0.15)	0.24(0.19)	0.18(-0.75-1.11)	0.37(0.18)	0.36(0.12)	0.07(-0.85-0.99)



	Paretic side			Non-paretic side		
	Baseline	Imposed Spatial Sym.	ES (95% CI)	Baseline	Imposed Spatial Sym.	ES (95% CI)
KFM	0.19(0.08)	0.15(0.03)	0.66(-0.61-1.93)	0.43(0.17)	0.40(0.22)	0.15(-1.09-1.39)

Figure 5-6: Mean knee joint moments (peak KFM) for stroke survivors (red diamonds) and 95% confidence intervals by whiskers at baseline and after imposing temporal (panel A) and spatial symmetry (panel B). Individual means for each stroke survivor are represented by individual circles for the paretic side (P) (purple and green) and non-paretic side (NP) (yellow and blue) for A) imposed temporal symmetry and B) imposed spatial symmetry. Horizontal dashed lines represent the observed upper and lower 95% confidence intervals limits of healthy control participants (n=18) walking at SS (red) and 0.8 m/s (black) speeds. The tables present the observed overall mean (SD) and effect size (ES) of KFM of stroke survivors' (Baseline and after imposing temporal and spatial symmetries) paretic and non-paretic sides.

5.3.3 Imposing Swing time and Step Length Asymmetry on Stroke Survivors Who are Symmetrical at Baseline

5.3.3.1 Spatiotemporal Parameters of the Imposition of Swing time and Step Length Asymmetry

The spatiotemporal parameters, after imposing a swing time and step length asymmetry ratio on sub-groups of stroke survivors with symmetrical gait at baseline, are presented in Table 5-3. When walking in time with the metronome, the swing-time ratio imposed on the ***temporal symmetry*** sub-group was increased by 18% (the paretic side being assigned as the long-swing side). Imposing swing time asymmetry on the ***temporal symmetry*** sub-group caused the participants to slow down by 14.7%. Meanwhile, the step length ratio of the spatial symmetry sub-group was increased by 13.3% (the paretic side being assigned as the long step length side). Meanwhile, imposing step length asymmetry on the ***spatial symmetry*** sub-group caused the participants to slow down by 4.8%.

In the ***temporal*** and ***spatial symmetry*** sub-groups, pelvic obliquity was slightly increased on the paretic side and reduced on the non-paretic side, compared to the baseline observed during walking under imposed asymmetry. However, the pelvic obliquity found in the ***spatial symmetry*** sub-group on the paretic side was greater than in the healthy controls. In contrast, knee flexion angles did not change from the baseline during walking with imposed spatial or temporal asymmetry. However, the knee flexion angle on the paretic side was approximately 10° lower than in the healthy controls, which is a remarkable difference. Despite the fact that the toe-out angles did not display a remarkable change after imposing swing time and step length asymmetry, the toe-out angle on the paretic side in the ***temporal symmetry*** sub-group increased by over 2°, when walking with imposed asymmetry. However, in the temporal asymmetry sub-group, the toe-out angle on the non-paretic side was approximately 5° lower than in the healthy controls (see Table 5-3).

Table 5-3: Mean (SD) gait data for the stroke survivor sub-groups at baseline (symmetrical conditions), after imposing swing time and step length asymmetry. Negative pelvic obliquity values indicate frontal drop in the ASIS marker on the swing side, with respect to the horizontal plane. The text highlighted in red refers to the variables imposed under each condition (SS) Self-Selected walking speed. (ES) Effect Size.

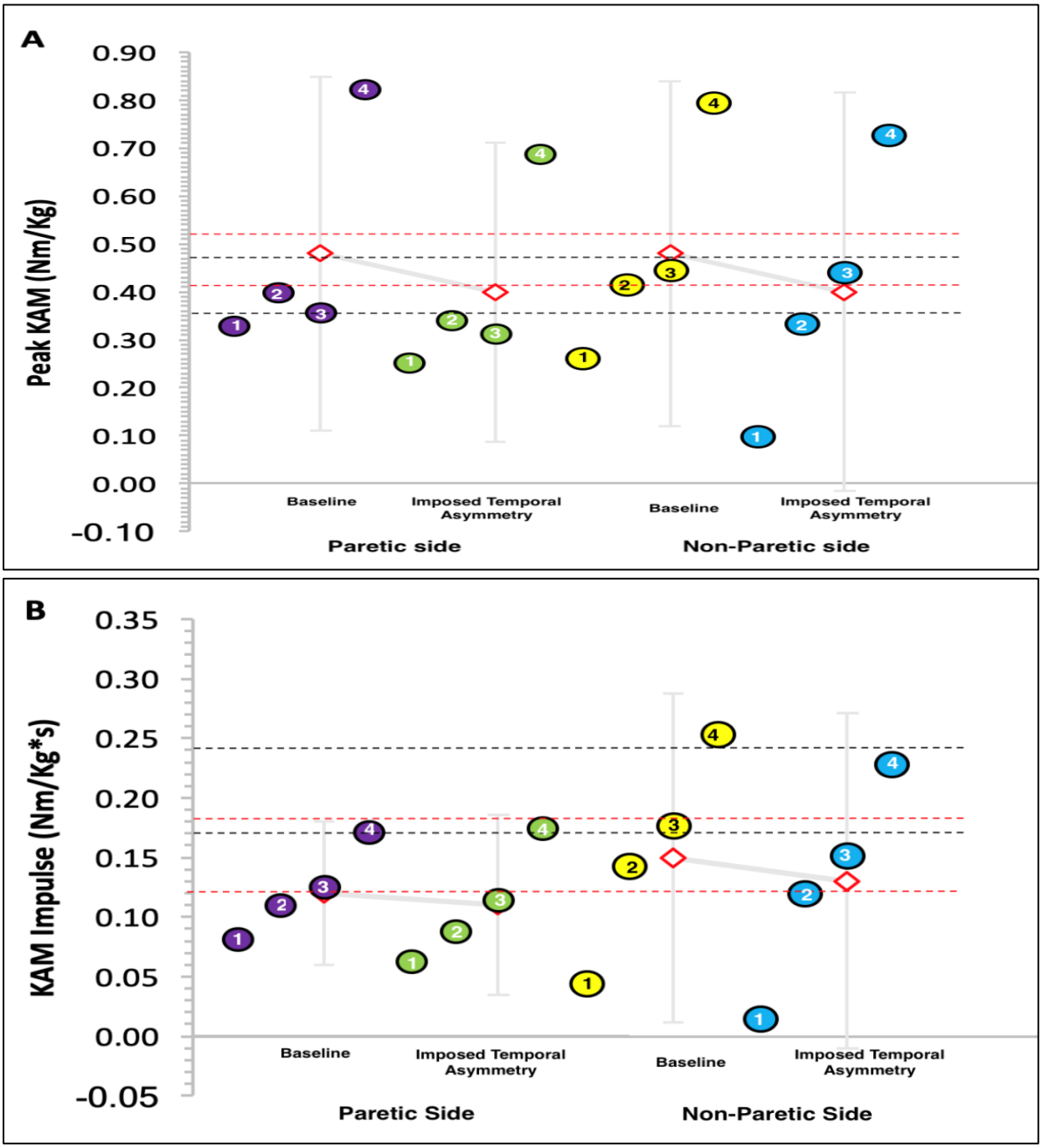
	Temporal symmetry (n=4)			Spatial symmetry (n=5)			Healthy control (13)	
	Baseline	Induced asymmetry	ES (95% CI)	Baseline	Induced asymmetry	ES (95% CI)	SS	0.8 m/s
Walking speed (m/s)	1.16(0.09)	0.99(0.13)	1.50(-0.07-3.07)	1.04(0.18)	0.99(0.21)	0.26(-0.98-1.50)	1.28(0.2)	0.90(0.14)
Symmetry ratio								
Swing time	1.04(0.01)	1.21(0.21)	1.14(-0.35-2.63)	1.18(0.14)	1.21(0.19)	0.20(-1.04-1.44)	1.04(0.01)	1.02(0.01)
Step length	1.04(0.02)	1.18(0.10)	1.94(0.26-3.62)	1.05(0.03)	1.19(0.08)	2.32(0.72-3.92)	1.04(0.03)	1.06(0.07)
Pelvic obliquity angle (at time of peak KAM) (°)							-3.71(2.51)	-2.66(2.80)
Paretic	-2.69(1.87)	-1.53(2.32)	0.55(-0.86-1.96)	-0.62(4.88)	0.51(5.43)	0.22(-1.02-1.46)		
Non-Paretic	-1.30(3.20)	-2.27(1.07)	0.41(-0.99-1.81)	-1.86(1.96)	-3.07(2.03)	0.61(-0.66-1.88)		
Knee flexion angle (°)							45.54(5.67)	45.00(6.52)
Paretic	41.54(3.20)	40.15(8.85)	0.21(-1.18-1.60)	34.04(9.21)	35.24(11.69)	0.11(-1.13-1.35)		
Non-Paretic	47.12(10.70)	48.63(12.55)	0.13(-1.26-1.52)	45.32(10.23)	48.11(10.76)	0.27(-0.98-1.52)		
Toe-out angle (°)							15.47(5.83)	14.68(6.77)
Paretic	11.87(11.07)	14.27(11.05)	0.30(-1.09-1.69)	14.43(10.08)	14.98(10.48)	0.05(-1.19-1.29)		
Non-Paretic	12.54(11.01)	10.98(9.07)	0.16(-1.23-1.55)	16.93(7.08)	14.31(6.16)	0.40(-0.85-1.65)		

5.3.3.2 KAM after Imposing Swing Time Asymmetry on the Temporal Symmetry Sub-group

At baseline, peak KAM on the paretic and non-paretic sides in the ***temporal symmetry*** sub-group was comparable to that of the healthy controls, walking at SS speeds. In contrast, peak KAM on both the paretic and non-paretic sides was marginally higher than the upper limit of the healthy controls' 95% CI, while walking at 0.8 m/s. The imposition of swing time asymmetry reduced peak KAM on the paretic and non-paretic sides by 16.7% and 9.1%, respectively, compared to the symmetrical baseline conditions. However, reduced peak KAM on the paretic and non-paretic sides, after imposing swing time asymmetry, caused an overall decrease of 9% in the asymmetry of peak KAM between the paretic and non-paretic sides, compared to baseline conditions. After imposing swing time asymmetry, while peak KAM on the paretic and non-paretic sides was comparable to that of healthy controls, walking at 0.8 m/s, it had marginally decreased to below the lower limit of the healthy controls' 95% CI, walking at SS speeds (see Figure 5-7a).

At baseline, while the KAM impulse on the paretic side in the ***temporal symmetry*** sub-group was more or less comparable to the lower limit of the healthy controls' 95% CI, walking at SS speeds, KAM impulse on the non-paretic side was comparable to that of the healthy controls,

walking at SS speeds. In contrast, KAM impulse on both the paretic and non-paretic limbs was lower than the lower limit of the healthy controls' 95% CI, walking at 0.8 m/s and at SS speeds. The imposition of swing time asymmetry slightly reduced peak KAM on both sides (more so on the non-paretic side), leading to a minor decrease of 5.5% in peak KAM asymmetry between the paretic and non-paretic sides, compared to the symmetrical baseline conditions. After imposing swing time asymmetry, despite the fact that the KAM impulse on the non-paretic side remained comparable to that of the healthy controls, walking at SS speeds, the paretic side showed a marginally reduced KAM impulse, below the lower limit of the healthy controls' 95% CI, walking at SS speeds (see Figure 5-7b).



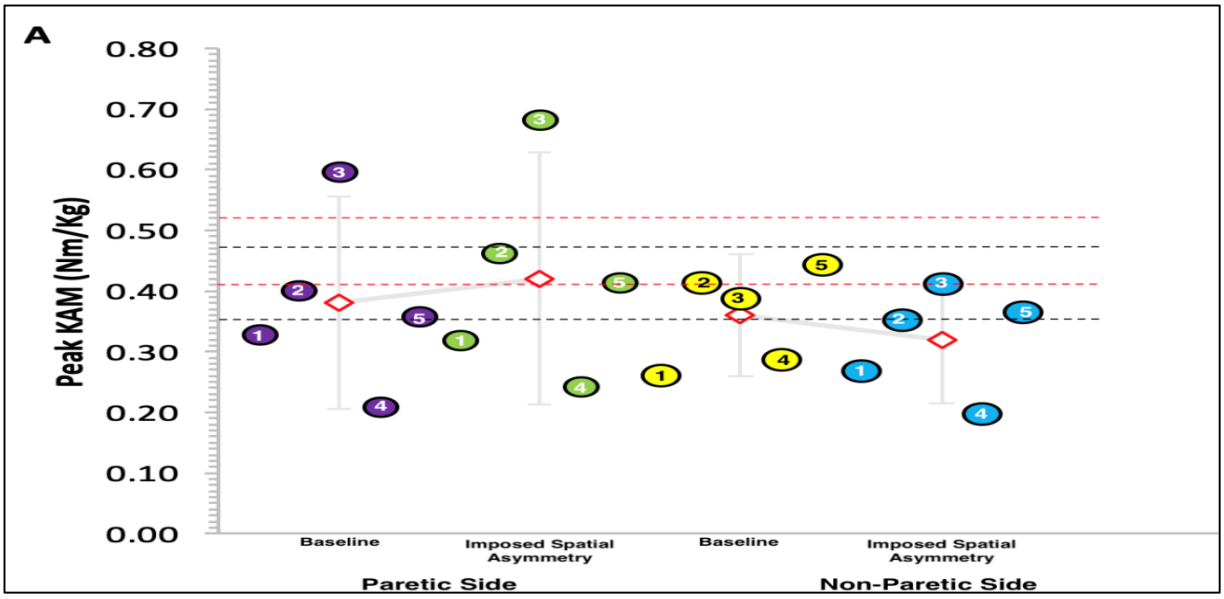
	Paretic side			Non-paretic side		
	Baseline	Imposed Temporal ASym.	ES (95% CI)	Baseline	Imposed Temporal ASym.	ES (95% CI)
Peak KAM	0.48(0.23)	0.40(0.20)	0.37(-1.03-1.77)	0.48(0.23)	0.40(0.26)	0.33(-1.07-1.73)
KAM Impulse	0.12(0.04)	0.11(0.05)	0.22(-1.17-1.61)	0.15(0.09)	0.13(0.09)	0.22(-1.17-1.61)

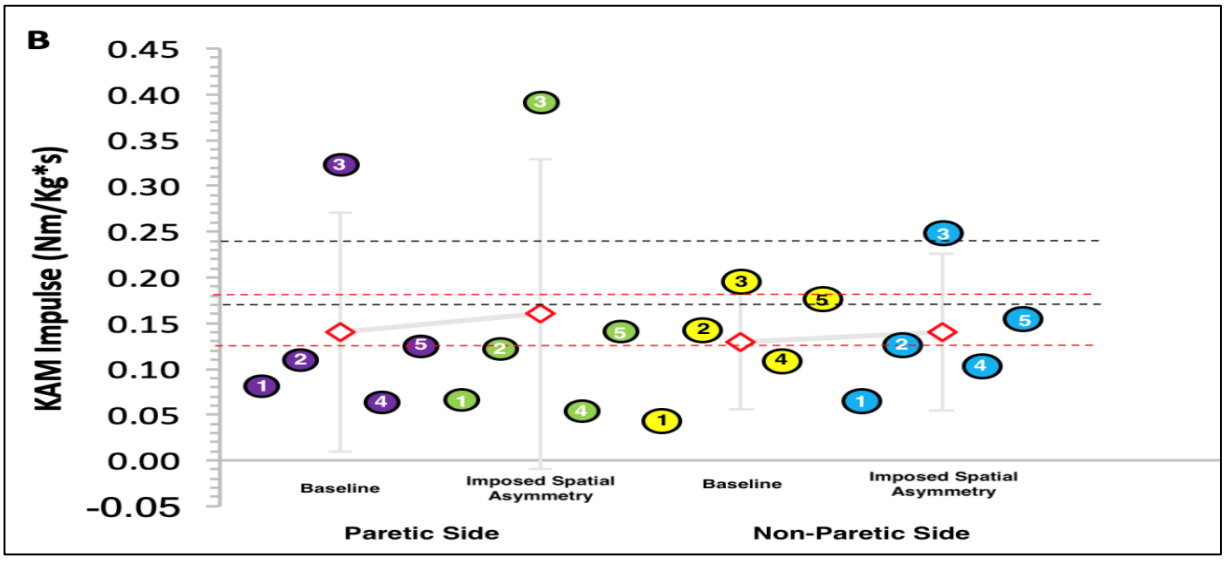
Figure 5-7: Mean knee joint moments (peak KAM and Impulse) in the stroke survivors (red diamonds) and 95% CI, indicated by whiskers at baseline and after imposing temporal asymmetry – individual means for each stroke survivor are represented by individual circles for the paretic ([P], purple and green) and non-paretic ([NP], yellow and blue) sides, for A) Peak KAM, and B) KAM impulse. Horizontal dashed lines represent the observed upper and lower limits of the 95% CI of the healthy controls (n=10), walking at SS speeds (red) and 0.8 m/s (black). The table presents the observed overall mean (SD) and effect size (ES) of KAM and KAM impulse of stroke survivors' (Baseline and after imposing spatial symmetry) paretic and non-paretic sides.

5.3.3.3 KAM after Imposing Step Length Asymmetry on the Spatially Symmetrical Sub-group

Baseline peak KAM on the paretic and non-paretic sides of the *spatial symmetry* sub-group was comparable to that of the healthy controls, walking at 0.8 m/s, but below the lower limit of the healthy controls' 95% CI, walking at SS speeds. Imposing step length asymmetry caused a marginal increase in peak KAM on the paretic side, compared to the stroke survivors' baseline, while peak KAM on the non-paretic side was slightly reduced. However, the slightly increased peak KAM on the paretic side and the slightly reduced peak KAM on the non-paretic side, after imposing step length asymmetry, caused an overall increase of 24% in the asymmetry of peak KAM between the paretic and non-paretic sides, compared to baseline conditions. After imposing step length asymmetry, despite the fact that peak KAM on the paretic side remained comparable to that of the healthy controls, walking at 0.8 m/s, a marginal increase in peak KAM was observed; becoming comparable to that of the healthy controls, walking at SS speeds. However, peak KAM on the non-paretic side was reduced below the lower limit of the healthy controls' 95% CI, walking at 0.8 m/s (see Figure 5-8a).

At baseline, KAM impulse on the paretic and non-paretic sides in the *spatial symmetry* sub-group was comparable to that of the healthy controls, walking at SS speeds, but below the lower limit of the healthy controls' 95% CI, while walking at 0.8 m/s. The imposition of step length asymmetry marginally increased KAM impulse on both sides (more so on the paretic side), causing an increase of 6% in KAM impulse asymmetry between the paretic and non-paretic sides, compared to asymmetry under the baseline conditions. After imposing step length asymmetry, the increased KAM impulse on the paretic and non-paretic sides failed to bring about any appreciable change, in comparison to healthy controls, walking at 0.8 m/s and SS speeds (see Figure 5-8b).





	Paretic side			Non-paretic side		
	Baseline	Imposed Spatial ASym.	ES (95% CI)	Baseline	Imposed Spatial ASym.	ES (95% CI)
Peak KAM	0.38(0.14)	0.42(0.17)	0.26(-0.98-1.50)	0.36(0.08)	0.32(0.09)	0.47(-0.79-1.73)
KAM Impulse	0.14(0.10)	0.16(0.14)	0.16(-1.08-1.40)	0.13(0.06)	0.14(0.07)	0.15(-1.09-1.39)

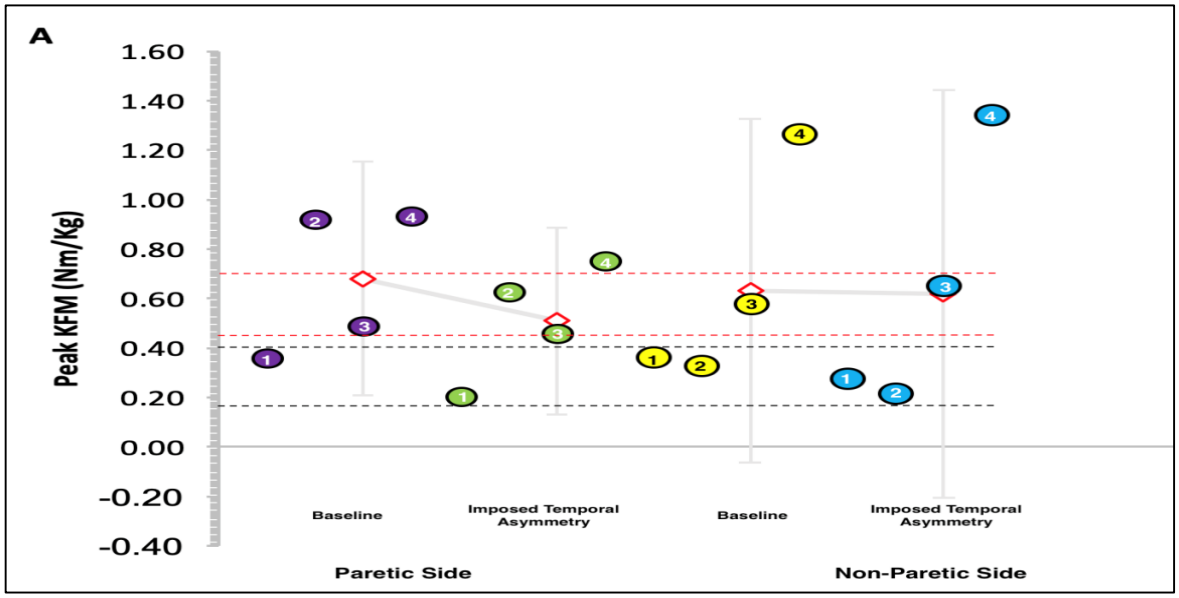
Figure 5-8: Mean knee joint moments (peak KAM and KAM impulse) in the stroke survivors (red diamonds) and 95% CI, indicated by whiskers at baseline, as well as after imposing spatial asymmetry – individual means for each stroke survivor are represented by individual circles for the paretic ([P], purple and green) and non-paretic ([NP], yellow and blue) sides, for A) Peak KAM, and B) KAM impulse. Horizontal dashed lines represent the observed upper and lower 95% CI limits of the healthy controls (n=10), walking at SS speeds (red) and 0.8 m/s (black). The table presents the observed overall mean (SD) and effect size (ES) of KAM and KAM impulse of stroke survivors' (Baseline and after imposing spatial symmetry) paretic and non-paretic sides.

5.3.3.4 KFM after Imposing Swing Time Asymmetry on a Temporally Symmetrical Sub-group

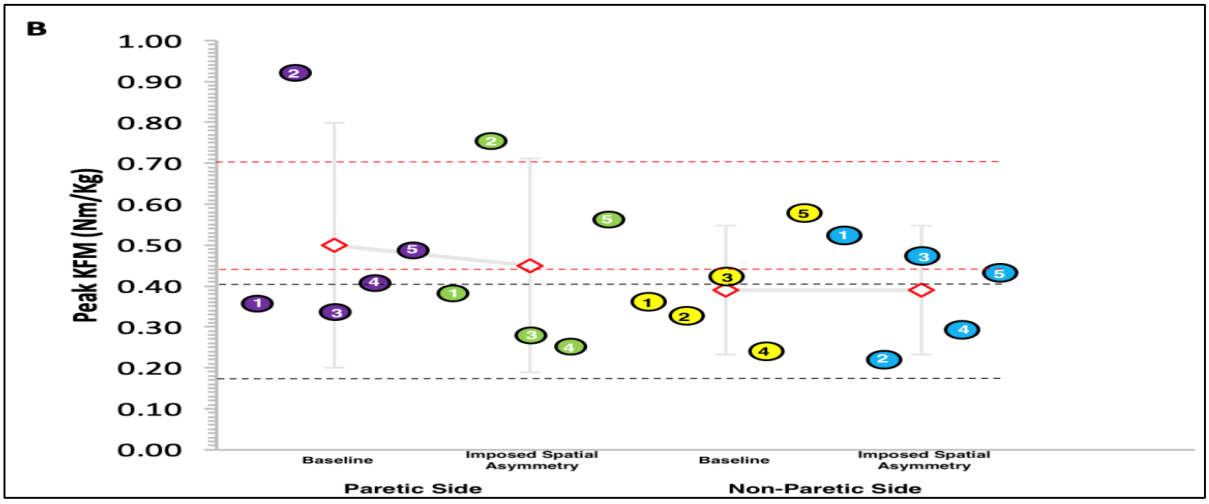
Baseline peak KFM on the paretic and non-paretic sides in the ***temporal symmetry*** sub-group was comparable to that of the healthy controls, walking at SS speeds, but higher than the upper limit of the healthy controls' 95% CI, while walking at 0.8 m/s. The imposition of swing time asymmetry reduced peak KFM on the paretic side by 32.4%, namely to a remarkable extent compared to the baseline conditions, while the non-paretic side showed no change. However, reduced peak KFM on the paretic side caused an overall increase of 15% in the asymmetry of peak KFM between the paretic and non-paretic sides, compared to the baseline conditions. After imposing swing time asymmetry, peak KFM on the paretic side failed to cause any remarkable change, compared to healthy controls, walking at SS speeds. In contrast, peak KFM on the paretic side had reduced from what was observed during walking at baseline, compared to healthy controls, walking at 0.8 m/s (see Figure 5-9a).

5.3.3.5 KFM after Imposing Step Length Asymmetry on the Spatially Symmetrical Sub-group

Baseline peak KFM on the paretic side in the ***spatial symmetry*** sub-group was comparable to that of the healthy controls at baseline, walking at SS speeds, but higher than the upper limit of the healthy controls' 95% CI, walking at 0.8 m/s. In contrast, peak KFM on the non-paretic side was comparable to that of the healthy controls, walking at 0.8 m/s, and below the lower limit of the healthy controls' 95% CI, walking at SS speeds. Imposing step length asymmetry reduced peak KFM on the paretic side by 10%, compared to baseline conditions, while the non-paretic side showed no change. However, reduced peak KFM on the paretic side caused an overall decrease of 9.8% in the asymmetry of peak KFM between the paretic and non-paretic sides, compared to baseline conditions. After imposing step length asymmetry, peak KFM on the paretic side failed to cause any remarkable change, compared to the healthy controls, walking at SS speeds. In contrast, peak KFM on the paretic side was reduced from what was observed at baseline during walking, compared to healthy controls, walking at 0.8 m/s (see Figure 5-9b).



	Paretic side			Non-paretic side		
	Baseline	Imposed Temporal ASym.	ES (95% CI)	Baseline	Imposed Temporal ASym.	ES (95% CI)
KFM	0.68(0.30)	0.51(0.24)	0.63(-0.79-2.05)	0.63(0.44)	0.62(0.52)	0.02(-1.37-1.41)



	Paretic side			Non-paretic side		
	Baseline	Imposed Spatial ASym.	ES (95% CI)	Baseline	Imposed Spatial ASym.	ES (95% CI)
KFM	0.50(0.24)	0.45(0.21)	0.22(-1.02-1.46)	0.39(0.13)	0.39(0.13)	0.00(-1.24-1.24)

Figure 5-9: Mean knee joint moments (peak KFM) for stroke survivors (red diamonds) and 95% confidence intervals by whiskers at baseline and after imposing temporal (panel A) and spatial asymmetry (panel B). Individual means for each stroke survivor are represented by individual circles for the paretic side (P) (purple and green) and non-paretic side (NP) (yellow and blue) for A) imposed temporal asymmetry and B) Imposed spatial asymmetry. Horizontal dashed lines represent the observed upper and lower 95% confidence intervals limits of healthy control participants (n=18) walking at SS (red) and 0.8 m/s (black) speeds. The tables present the observed overall mean (SD) and effect size (ES) of KFM of stroke survivors' (Baseline and after imposing temporal and spatial symmetries) paretic and non-paretic sides.

5.4 Discussion

To the author's knowledge, this is the first study to ***investigate the immediate effects*** of changing spatiotemporal symmetry/asymmetry on knee joint loading patterns (joint moment) in stroke survivors. The importance of this study lies in the various rehabilitation approaches adopted (D. S. Reisman et al., 2013; Teixeira-Salmela et al., 2001; Wright et al., 2013), with the aim of improving spatiotemporal asymmetry and thereby enhancing outcomes such as the aesthetics of walking (Vasudevan and Kirk, 2014; Winstein et al., 2016), and minimising mechanical and metabolic inefficiencies, as well as the hypothesised risk of joint wear-and-tear (K. K. Patterson et al., 2008). However, it is not known to what extent the promotion of symmetrical gait patterns in stroke survivors affects knee joint loads. Moreover, it is widely thought that gait asymmetry increases stance time on the unaffected limb and consequently, loading – which is known to be risk factor for the development of OA (Jones et al., 2013; Lloyd et al., 2010). The implicit assumption that spatiotemporal asymmetry leads to knee loading patterns that are indicative of the development of knee OA has not been tested previously. Therefore, this study has sought to establish causality in the immediate effect of spatiotemporal symmetry/asymmetry on knee loading amongst stroke survivors and healthy participants.

The results of this study show that imposing symmetry on stroke survivors with temporal asymmetry causes knee moments on the paretic side to remain higher than on the non-paretic side, leading to a number of smaller increases, which exceed those observed in healthy controls. In contrast, no changes were observed in knee joint moment across other gait conditions. The possible reason for this small effect on knee joint moment is the demonstrated nature of spatiotemporal asymmetry, in its relative resistance to change (on the imposition of symmetry).

5.4.1 Effects of Imposing Temporal Symmetry on Knee Joint Moment amongst Stroke Survivors

After imposing swing time symmetry ***(accomplished by 16% of the swing time baseline)*** on participants with temporal asymmetry, peak KAM showed minimal increase (9%) on the paretic side (the vast majority of the stroke survivors [60%] displaying peak KAM in excess of

the upper limit of healthy controls' 95% CI), and minimal decrease (8%) on the non-paretic side, causing an overall increase (20%) in peak KAM asymmetry. However, KAM impulse did not manifest in any remarkable changes. The peak KAM asymmetry between sides may perhaps be explained by the contribution of the paretic side to prolonged paretic swing time and reduced reliance on non-paretic stance during walking (Liu et al., 2008; K. K. Patterson et al., 2008; Peterson et al., 2010). According to Kim and Eng (2003), an increase in paretic swing time is positively correlated with an increase in GRF on the non-paretic side. Accordingly, this may increase both stance time and GRF on the paretic side, thereby increasing paretic peak KAM.

Unlike KAM, KFM did not change appreciably in response to the imposition of swing time symmetry. It is well accepted that walking speed (Ardestani et al., 2016; van den Noort et al., 2013; Zeni and Higginson, 2009) and knee RoM during stance (Creaby et al., 2013; Ho et al., 2012) determines changes in KFM during walking. Therefore, the fact that there were no changes in KFM in the current study is likely to be due to consistency in these variables compared to baseline (asymmetrical) conditions. Although peak KFM was asymmetrical between the stroke survivors' paretic and non-paretic sides, this joint moment was comparable to that of healthy controls, walking at a slow speed, but lower than in healthy controls, walking at SS speeds. This provides further evidence of the contribution of speed to the differences in peak KFM, which were observed between the groups (Zeni & Higginson, 2009; van den Noort et al., 2013), as an increase in walking speed was found to increase GRF and peak KFM.

The imposed swing time symmetry achieved in the stroke participants in this study was just 16%, compared to the baseline. This supports the results of the previous study, which reported the resistance of post-stroke temporal asymmetry to change (S. L. Patterson et al., 2008). Accordingly, it may explain the small effect of imposing swing time symmetry on knee joint moment in the current study. Future studies with high intensity training in gait symmetry are therefore necessary.

Impact statements:

KAM was minimal after imposing swing time symmetry on stroke survivors with temporal asymmetry, accounting for less than 10% on each side. KFM did not manifest in notable changes. However, the relatively high resistance of temporal asymmetry to change and compensatory mechanisms may play an important role in counteracting further moment changes.

5.4.2 Effects of Imposing Temporal Asymmetry on Temporally Symmetrical Stroke Survivors

After imposing swing time asymmetry, peak KAM on both sides in the stroke survivors ***decreased*** (by 16%) from baseline (symmetrical) conditions (but remained within the 95% CI of the healthy participants). One possible explanation for this (de David et al., 2015; Robbins and Maly, 2009) might be that the stroke survivors walked more slowly (speed reduced by 16%), when walking under the imposition of temporal asymmetry, compared to the baseline conditions. In the stroke survivors who were temporally symmetrical at baseline, KAM impulse was unchanged after imposing swing time asymmetry and remained below the healthy participants' lower 95% CI limit on both the paretic and non-paretic sides at baseline, while walking at a slow matched speed. This is despite the stroke survivors' slow walking speed, which would normally be expected to increase KAM impulse and KAM impulse asymmetry (de David et al., 2015; Robbins and Maly, 2009) (compared to healthy participants, walking at higher speeds). This indicates that even stroke survivors who have regained/maintained temporal symmetry may have some residual impairment (for example, reduced strength and GRF) and/or compensatory gait patterns that minimise knee joint load and weight-bearing while walking (Kim and Eng, 2003; Peterson et al., 2010; Bhavana Raja et al., 2012). Similar to KAM impulse, the imposition of swing time asymmetry on temporally symmetrical stroke survivors failed to change KFM from the baseline conditions.

Impact statements:

While it is widely thought that gait asymmetry increases load, there were no changes to knee joint moment after imposing temporal asymmetry on stroke survivors who had regained temporal symmetry.

5.4.3 Effects of Imposing Spatial Symmetry on Knee Joint Moment in Stroke Survivors

The imposition of step length symmetry ***(accomplished at 7% of the step length baseline)*** on participants with spatial asymmetry failed to change peak KAM, compared to the baseline conditions. This may be attributed to the small (7%) improvement in step length symmetry, achieved by stepping to foot-fall targets. The lack of improvement in spatial symmetry is consistent with previous evidence, where no change in inter-limb asymmetry was reported (despite changes in step length), after imposing step length symmetry on stroke survivors (Kahn and Hornby, 2009; S. L. Patterson et al., 2008). However, stroke survivors may require more than one training session to increase their step length symmetry by more than 7.4%. Another possible reason for the lack of change in peak KAM may be due to consistent pelvic movement. The pelvic obliquity (tilt) measured here did not change from the baseline; remaining higher on the paretic side and lower on the non-paretic side (drop). Consequently, peak KAM continued to be asymmetrical, even after an imposed increase in step length symmetry.

KAM impulse after imposing step length symmetry increased to a similar extent on both the paretic and non-paretic sides. While the increase in KAM impulse was comparable to that of the healthy controls, walking at a slow matched speed, it exceeded the upper limit of the healthy controls' 95% CI, walking at SS speeds. This increased KAM impulse may be attributed to a reduction in walking speed by 14.3% (de David et al., 2015; Robbins and Maly, 2009), compared to baseline conditions.

After imposing step length symmetry on the participants with spatial asymmetry, no systematic changes in KFM were observed (on either the paretic or non-paretic side), compared to the baseline conditions. Therefore, KFM remained asymmetrical between the sides under baseline conditions, as KFM on the non-paretic side was higher than on the paretic side and in the healthy controls, walking at a slow matched speed. However, these results contradict those of a study by Allen et al. (2011), who demonstrated that step length asymmetry has a causal effect on KFM; increasing it on the non-paretic side in stroke survivors. This difference in findings could be attributed to the minor improvement in step length symmetry and small sample size used in the current study (n=5).

5.4.4 Effects of Imposing Spatial Asymmetry on Spatially Symmetrical Stroke Survivors

After imposing step length asymmetry, the peak KAM of stroke survivors with spatial symmetry was increased on the paretic side and decreased on the non-paretic side, causing an overall increase in peak KAM asymmetry. Although peak KAM on the paretic side remained comparable with that of healthy controls, walking at a slow matched speed, peak KAM on the non-paretic side was below the 95% CI of speed-matched healthy controls. A possible explanation for the rise in peak KAM on the paretic side may be the increase in pelvic drop by 1° on the non-paretic side, compared to baseline conditions and the healthy controls. In contrast, the decrease in peak KAM on the non-paretic side was most likely due to the increase in pelvic tilt by 1°, compared to baseline conditions, and by 3°, compared to healthy controls (see Table 5-3).

For the stroke survivors who were spatially symmetrical at baseline, KAM impulse on both the paretic and non-paretic sides was unchanged and remained below the 95% CI of the healthy controls, walking at a slow matched speed. Despite the fact that stroke survivors walking slowly may be expected to increase their KAM impulse (de David et al., 2015; Robbins and Maly, 2009), additional impairments can serve to minimise knee joint load and weight-bearing during walking (Kim and Eng, 2003; Peterson et al., 2010; Bhavana Raja et al., 2012).

After imposing step length asymmetry, the KFM of stroke survivors with spatial symmetry was unchanged after imposing step length asymmetry, compared to baseline conditions. This result is contrary to Allen et al. (2011), where it was indicated that while walking with step length asymmetry, KFM increases on the short side in stroke survivors with a long step length on the paretic side. However, this conflict between studies is likely to be due to the small sample size used in this current study (n=5).

Impact statement:

Changing step length (by either imposing asymmetry or symmetry) does not change KAM or KFM in systematic or appreciable ways.

5.5 Limitations of the Study

The sample size of the small sub-groups yields proof-of-concept insights into the immediate effects of manipulating spatial and temporal symmetry in stroke survivors. Stroke survivors may require more than one training session to enhance their spatiotemporal symmetry by over 7-8% for step length and 16% for swing time. However, this minor change in spatiotemporal symmetry may or may not bring about an obvious alteration to the relevant joint load.

5.6 Future Work

The small and uneven sample sizes used in the stroke survivor sub-groups could have affected the accuracy of the results obtained, both between the stroke survivors and in comparison with the healthy controls. Therefore, it is important to investigate the effect of imposing spatiotemporal symmetry/asymmetry on knee joint load, using large and equally distributed sample sizes. This will contribute further understanding of stroke survivors' knee joint moments during walking. In addition, intensive walking practice in future work would help provide a meaningful adaptation to protocol, instead of immediate effects. In this current study, the presence of post-stroke impairment and inadequate/insufficient practice may have affected the participants' responses in adjusting their stepping to auditory and visual cues. Therefore, intensive practice would enable participants to modify their motor and sensory plans in response to changes in symmetry (D. S. Reisman et al., 2013). Consequently, this could give greater insight into stroke survivors' knee joint load after imposing the target symmetry. Nevertheless, although the stroke survivors in this study walked at a slow speed, the joint moment parameters were not as responsive as in the healthy controls. Therefore, investigating stroke survivors' knee joint load at different walking speeds should be considered in future work.

5.7 Conclusion

Knee joint moments ***do not manifest in notable changes*** as part of the immediate effect of either imposing symmetry or asymmetry on stroke survivors. Differences in the effect of

spatiotemporal asymmetry on knee joint moment may be due to 1) post-stroke compensatory gait patterns, interacting with spatiotemporal asymmetry to determine knee joint moments, or 2) the relatively high resistance of spatiotemporal asymmetry to change. Additionally, the influence of walking speed on knee joint moment was evident from the absence of any difference in knee joint moment between the stroke survivors and healthy controls, walking at comparable speeds. Thus, this study does not provide any support for concerns that spatiotemporal asymmetry may be responsible for abnormal mechanical loading of the knee joint. However, the results of this study still need to be viewed in light of the research limitations. Moreover, future investigation is necessary to determine the long-term effects of intensive practice on gait symmetry. This would provide satisfactory insights into knee joint load in stroke survivors after imposing improved symmetry.

Chapter 6: Knee Joint in Stroke Survivors over Time: A Case Series

This chapter reports on a retrospective case series study, aimed at characterising stroke survivors' knee joint load/moments over time (assessed on two occasions: at baseline and at a two-year follow-up).

6.1 Background

Strokes constitute a life-changing medical event, affecting a wide range of brain functions, and resulting in a variety of associated problems such as reduced motor and cognitive function, reduced participation, and long-term disability (Beyaert et al., 2015). The type, severity, and location of a stroke will determine the extent of the impairments and functional limitations that it incurs. As a result, the impairments suffered by stroke survivors are widely heterogeneous (Cramer et al., 2017; Meyer et al., 2015) and the pattern of recovery following stroke is a complex and multi-faceted process, characterised by wide variation between individuals. Although there is often severe neurological impairment and disability experienced in the early stages following a stroke, most stroke survivors achieve some degree of recovery over time (Cramer et al., 2017). However, the initial paresis grading is the most important predictor of the extent and duration of recovery (Hendricks et al., 2002).

Post-stroke, impaired movement receives the most attention in physical therapy (Langhorne et al., 2009). The ability of stroke survivors to regain basic movement/functional patterns is not straightforward and may follow different paths, with varying proportions of spontaneous, true recovery and compensation. However, there remain gaps in knowledge of how physiological, anatomical and behavioural aspects of recovery progress over time (Cramer et al., 2017). Thus, research on therapies that can improve quality of life for individuals as they pass through the different stages of a stroke is critical.

The process of spontaneous recovery unfolds within the first three months of onset of a stroke (Nudo, 2011). The mechanism of spontaneous recovery involves changes to the cellular and behavioural aspects of the brain, thus leading to some or (rarely) full recovery (Cramer, 2008). However, spontaneous recovery is more likely to occur in mildly stroke-impaired individuals, compared to those with severe deficits (Cramer, 2008).

While some spontaneous recovery can occur following a stroke, recovery is reinforced by rehabilitative efforts to maximise brain function (the restorative approach) and/or develop compensatory strategies, aimed at improving motor outcomes and overall functioning (Langhorne et al., 2009). It has been reported that most neurological recovery is witnessed within the first weeks-to-months following a stroke, reaching a plateau between three and six months (Verheyden et al., 2008). Although it is not clear whether early improvement can be sustained/increased over time, a recent longitudinal study (n=238) revealed significant post-stroke deterioration in long-term functioning and motor recovery, between six months and five years (Meyer et al., 2015). The potential for post-stroke recovery may be influenced by different factors such as the external environment, continuity of rehabilitation (carry-over), motivation for functional recovery, stroke pathogenesis, and lesion site in the case of neurological recovery (Lee et al., 2015). However, much of the literature on post-stroke gait is dominated by small cohorts and cross-sectional designs at various time points following stroke and there are few longitudinal studies on gait (just eight studies, with a total sample size of n=284), which span the years of survival that stroke survivors now achieve (Allen et al., 2011; Kim and Eng, 2004; Lee et al., 2015; Mahendran et al., 2016; Marrocco et al., 2016; Mercer et al., 2014; Patterson et al., 2014; Teixeira-Salmela et al., 2001).

Spatiotemporal asymmetry is one of the most frequently reported impairments amongst chronic stroke survivors (Patterson et al., 2014; K. K. Patterson et al., 2008). However, while spatiotemporal asymmetry has been well reported, there is little information in the literature about long-term longitudinal changes (over a period of years). Patterson et al. (2014) investigated changes (through retrospective chart reviews) in spatiotemporal symmetry and walking speed amongst stroke survivors (n=71) over time (up to >48 months) and throughout in-patient rehabilitation. The results demonstrated that swing time and step length asymmetry did not exhibit any change in the majority of asymmetrical stroke survivors within the timeframe (no change in swing time or step length symmetry in 79% and 86% of the subjects, respectively). Improved swing time symmetry was associated with increased weight-bearing on the paretic side, while improved step length was associated with an improvement in walking speed. In contrast, while 50% of the stroke survivors showed no change in walking speed, walking speed was significantly increased (by 30%) over time, compared to admission. However, the result of the above study must be interpreted with caution, because an in-

patient rehabilitation programme was not reported. The absence of changes in spatiotemporal gait asymmetry is therefore likely to be due to the lack of training specificity (S. L. Patterson et al., 2008; Darcy S. Reisman et al., 2013).

Following stroke, disturbed lower limb movement is associated with various gait abnormalities, such as kinematic and kinetic abnormalities (Chen et al., 2005; Marrocco et al., 2016; Rosa et al., 2014). Accordingly, deviation in kinematic and kinetic profiles (magnitude and pattern) has been consistently noted between these and those of non-disabled individuals (Chen et al., 2005; Cruz et al., 2009). Recovery in post-stroke gait biomechanics is thought to be important, because of its link to walking function and safety (Hall et al., 2011; Mulroy et al., 2003; Darcy S. Reisman et al., 2013). A number of studies have investigated changes in joint kinematics following a stroke, within sessions (Kesar et al., 2009; Kesar et al., 2015; Reissman et al., 2018) and over limited periods (less than six months) (Dean et al., 2000; Lewek et al., 2009; Mulroy et al., 2003; Mulroy et al., 2010; Yavuzer et al., 2007), in each case while walking. However, longitudinal kinematic changes (over a period of years) in stroke survivors' lower limbs during walking have not been investigated.

To date, kinetic measures of walking (i.e. knee joint moments) in stroke survivors have received relatively little attention (Allen et al., 2011; Kim and Eng, 2004; Marrocco et al., 2016; Teixeira-Salmela et al., 2001). Despite the persistence of post-stroke gait dysfunction, even long after rehabilitation, studies characterising knee joint moments (reflecting loading) over longer-term stroke recovery are lacking. Knee joint moments (KAM and KFM) are altered in a way that is known to indicate the risk of joint OA (Marrocco et al., 2016). These altered moments may result from slower walking speeds (Robbins and Maly, 2009), altered knee joint RoM, and muscle co-activation (Creaby et al., 2013; Farrokhi et al., 2015; Hutin et al., 2012). Additionally, compensatory gait patterns, such as hip hiking (Chiba et al., 2016; Dunphy et al., 2016; Linley et al., 2010), increased trunk lean (Van Criekinge et al., 2017), and toe-out and toe-in (Shull et al., 2013) are also known to contribute to changes to knee joint moments during walking (Shull et al., 2013).

The majority of stroke survivors achieve independent ambulation (Alexander et al., 2009), but their gait tends to be characterised by alternation/asymmetry in most of its biomechanical aspects, due to persistent impairment (Patterson et al., 2014). Consequently, this may be

connected with numerous undesirable issues, such as challenges to balance control, increased energy expenditure, increased risk of musculoskeletal injury to the lower extremities, and a decrease in overall activity (Hendrickson et al., 2014; Patterson and Sibley, 2016). Therefore, it is important to identify the long-term biomechanical mechanism or changes that underlie stroke-related gait patterns, in order to enhance the efficacy and success of rehabilitation strategies following injury.

Following stroke, altered gait mechanics constitute just one factor of the potential risk of developing knee joint OA. Other risk factors of knee OA that stroke survivors share include age, high BMI and altered tissue responses to new/impaired gait mechanics (Marini et al., 2001; Sheffler et al., 2014). Persistent post-stroke alterations in gait pattern may play a role as mechanical stimuli, which provoke biological processes that underlie the development of OA (Andriacchi et al., 2015). With steady improvement in long-term survival after stroke (Boysen et al., 2009), stroke survivors subsequently face a greater number of years of cumulative exposure to biomechanical (spatiotemporal symmetry, kinematics and kinetics) and biological (increased age and BMI) changes, which may mean that their knee joints become less able to adapt to excessive/repetitive loading, thus leading to knee OA. Studies have reported increased pain (Hettiarachchi et al., 2011) and reduced femoral cartilage thickness on the paretic side in stroke survivors, compared to healthy individuals (Tunc et al., 2012). This suggests that following stroke, tissues may not adapt well to stroke-related changes in joint load.

Nevertheless, the cause of pain and cartilaginous change has not yet been identified. Therefore, at least two years is required to observe the long-term effects of gait impairment on joint tissues and structures (Yang et al., 2005). Accordingly, longitudinal studies are required to examine the course of changes in gait biomechanics amongst stroke survivors over time. Given that one study on spatiotemporal asymmetry in stroke survivors revealed no changes (i.e. no improvement) to gait asymmetry in the years following stroke, these persistent changes to gait would appear to interact with the biological processes of disease development – biology that takes years to progress. Therefore, there is a need to examine the biomechanics longitudinally, in order to observe the long-term effect of altered gait pattern on the knee joint in stroke survivors.

Although quantity limb-loading during post-stroke gait is feasible (Marrocco et al., 2016), there is still a lack of published follow-up data (collected over a period of years) for most of the biomechanical variables that specifically relate to knee joint moment. Thus, the long-term prognosis and outcomes for knee joint moment in stroke survivors have not yet been revealed. Therefore, the aim of this case series study is to characterise stroke survivors' knee joint load/moments over time (assessed on two occasions: at baseline and at a two-year follow-up).

6.2 Methods

This retrospective case series study is based on an analysis of secondary data gathered from a group of recruited stroke survivors, who had already participated in two previous studies, where initial measurements were taken (see Chapter 4: 1st Study), followed by these measurements being repeated at a two-year follow-up (see Chapter 5: 2nd Study).

6.2.1 The Participants

The same inclusion and exclusion criteria were applied to each study participant, and all the participants were subjected to the same functional measures (see section 3.1).

6.2.2 Procedure

The procedures for this study were similar to those applied in the previous study (see section 3.3). To clarify, the stroke survivors were fitted with single reflective passive and cluster markers, using the CAST marker model. They then walked along a six-metre walkway for a minimum of five trials. Kinetic data were obtained from embedded force plates, while spatiotemporal and kinematic data were collected using a motion capture system.

6.2.3 Statistical Analysis

For changes in knee joint moment between two visits, descriptive statistics (i.e. mean and standard division) were calculated for each variable. Swing time and step length symmetry ratios were determined for each stroke patient to evaluate changes in symmetry between the paretic and non-paretic side over time. Swing time and step length symmetry ratios are calculated as the ratio between the two legs (maximum/minimum). The direction of

asymmetry was determined according to the side that displayed greater swing time and step length values.

Prior to statistical analysis, dependent variables were tested for normality using Shapiro-Wilk tests (see appendix A.6). A paired t-test (α=0.05) was performed for all the participants at each visit to evaluate the difference in demographic, spatiotemporal, kinematic and kinetic data. ES, using the Cohen's *d* method (Cohen, 1992), was calculated using G*Power Version 3.1.1 (Universität Kiel, Germany). The corresponding 95% CI of ES was also provided by using the following formula (Lee, 2016):

$$\sigma(d) = \sqrt{\frac{N_1+N_2}{N_1 \times N_2} + \frac{d^2}{2(N_1+N_2)}}$$

$$95\%\ \text{CI for Cohen's } d\text{: } [d - 1.96 \times \sigma(d),\ d + 1.96 \times \sigma(d)]$$

(N: The sample size of group 1 and 2)

6.3 Results

6.3.1 The Participants and Clinical Assessments

A total of 9 stroke survivors (male=6) were recruited for this study. Demographic data and clinical assessment scores for each stroke survivor are presented in Table 6-1, below. The average age of these participants at the initial measurement (Visit 1 [V1]) was 64.6 years, based on an age range of 61-84, and 5 out of the 9 participants had experienced left-sided hemiplegia for a mean (± SD) duration of 86.3 months (±174.5) since the onset of stroke. At the initial measurement, the stroke survivors' mean body mass index (BMI) was 25.8 (±3.5), which showed no significant deviation over time (Visit 2 [V2]).

Although 3 out of 9 stroke survivors (S3, S7, S8) demonstrated a high degree of muscle tone on planter flexion of the ankle joint (MAS Achilles) at V1, the majority displayed stability in their muscle tone over time, except for S1, who developed 200% spasticity in the planter flexors. However, the MAS Quad values recorded indicated that most of the participants showed no change in joint muscle tone, except for S3 and S4, who displayed reduced spasticity in the knee flexors. Using ≥ 14 s as the threshold indicating high risk of fall in the TUG test, 3 participants (S4, S6, S8) displayed a high risk of fall at V1. However, while most of

the participants showed very little change by V2, 2 participants (S1, S6) presented with an increased TUG time of 52% and 30%, respectively.

Meanwhile, one stroke survivor (S5), with the longest time since the onset of stroke, was experiencing knee joint pain, which increased between V1 and V2. However, all the participants presented with good balance (BBS > 41) at the initial visit, except for S4, who had a low balance score of 38. Nevertheless, most of the stroke survivors demonstrated an increase in their balance scores over time, except for S1 and S8, who showed some deterioration. According to the Fugl-Meyer lower limb assessment, all the stroke survivors displayed residual paresis, as none scored the maximum at initial measurement. Conversely, while most of the participants showed stability in the Fugl-Meyer assessment at V2, 2 stroke survivors (S2, S9) presented with the maximum score of 34, and 1 (S1), with a deterioration of 30%. Low ES was observed between visits in the demographic and functional measures (value ranging from 0.03 to 0.21), except for the Fugl-Meyer assessment (sensation), which had a large ES (0.79).

Table 6-1: Demographic data

Participant No.	S1		S2		S3		S4		S5		S6		S7		S8		S9		Overall		P value	ES (95% CI)
	V1	V2	V1	V2	V1	V2	V1	V 2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2		
Age (years)																			64.6(8.5)			
Sex																			3 Female/ 6 Male			
Affected leg	R		L		L		L		R		L		R		L		R		4 Right / 5 Left			
Height (m)	1.55		1.65		1.78		1.45		1.70		1.79		1.68		1.78		1.83		1.69(0.1)			
Mass (Kg)	51	53	80	82	72	75	64	63	87	90	76	75	67	66	78	80	90	89	73.9(12.1)	74.8(12.3)	.184	0.07(-0.85-0.99)
BMI	21.2	22.4	29.4	30.1	22.5	23.7	30.4	30.0	30.10	31.1	23.7	23.7	23.7	23.4	24.6	25.5	26.9	26.6	25.8(3.5)	26.3(3.4)	.075	0.15(-0.78-1.08)
Time since stroke (Months)	22.0	44.0	11.0	32.0	14.0	35.0	15.0	38.0	548.0	561.0	64.0	85.0	69.0	91.0	19.0	43.0	15.0	38.0	86.3(174.5)	107.4(171.5)	.000	0.12(-0.80-1.04)
MAS-Achilles	0.00	2.00	0.00	0.00	2.00	1.50	1.00	1.00	0.00	0.00	0.00	0.00	3.00	3.00	3.00	3.00	0.00	0.00	1.00(1.3)	1.17(1.3)	.500	0.13(-0.79-1.05)
MAS_Quad	0.00	0.00	0.00	0.00	1.00	0.00	2.00	1.00	0.00	0.00	0.00	0.00	1.50	1.50	2.00	2.00	0.00	0.00	0.72(0.9)	0.50(0.8)	.170	0.26(-0.67-1.19)
TUG (s)	10.6	22.0	12.0	9.7	11.7	12.4	26.5	22.2	12.9	11.5	15.7	22.1	13.7	13.1	16.6	17.4	9.6	8.8	14.4(5.1)	15.5(5.5)	.510	0.21(-0.72-1.14)
KOOS	100	100	100	100	100	100	100	100	91.67	88.89	100	100	100	100	100	100	100	100	99.1(2.8)	98.8(3.7)	.350	0.09(-0.83-1.01)
BBS (0-56)	54.0	47.0	53.0	54.0	55.0	56.0	38	38	53	53	46	50	51	53	48	45	56	56	50.4(5.7)	50.2(5.9)	.840	0.03(-0.89-0.95)
Fugl-Meyer lower limb (0-34)	30.0	21.0	31.0	34.0	26.0	27.0	24.0	24.0	22.0	22.0	32.0	33.0	20.0	24.0	25.0	28.0	28.0	34.0	26.4(4.1)	27.4(5.2)	.500	0.21(-0.72-1.14)
Fugl-Meyer_ Sensory (0-12)	10.0	12.0	12.0	12.0	10.0	12.0	10.0	10.0	10.0	12.0	10.0	12.0	12.0	12.0	12.0	10.0	12.0	12.0	10.8(1.1)	11.6(0.9)	.190	0.79(-0.17-1.75)

Abbreviations: V: Visit; ES: effect size; Kg: Kilogram; BMI: Body Mass Index; MAS: Modified Ashworth Scale; TUG: Time Up&Go; KOOS: Knee Osteoarthritis outcome score; BBS: Berg Balance Scale; (m): meter; (s); second.

6.3.2 Spatiotemporal Data

Walking speeds and spatiotemporal parameters were observed in the stroke survivors, both at the initial measurement and over time, as presented in Table 6-2.

Using the walking speed threshold outlined by Perry et al. (1995) for a stroke population, the initial measurement at V1 revealed that 5 participants (S2, S3, S5, S7, S9) had unlimited outdoor mobility (walking speed >0.8 m/s); 2 participants (S1, S6) were limited outdoor walkers (walking speed=0.6-0.8 m/s); 1 stroke survivor (S8) was mobile indoors (walking speed=0.4-0.6 m/s), and 1 participant (S4) was not a functional walker (in daily life; walking speed<0.4 m/s). However, the majority of the stroke survivors showed an increase in walking speed of 3.6%-49% over a period of two years, although 2 participants (S1, S3) were 36% and 4.7% slower walkers, respectively, compared to the initial measurement.

At the initial measurement, using the cut-off ratio of the healthy population's swing time (1.06) and step length (1.08) symmetries (Patterson et al., 2010), 88.9% (8 out of 9) and 55.5% (5 out of 9) of the stroke survivors presented with swing time and step length asymmetry, respectively. They all displayed prolonged swing time on the paretic side and prolonged stance time on the non-paretic side. However, the direction of the step length asymmetry varied between them: 80% of those with step length asymmetry (4 out of 5) had a longer step length with the paretic limb.

Over time, while most of the stroke survivors with swing time asymmetry remained asymmetrical, the asymmetry ratio value decreased in 3 participants (S1, S2, S3) and increased in 5 participants (S4, S5, S6, S7, S8). For step length, the number of stroke survivors who showed asymmetry at V1 was reduced by 40% over time. For example, 3 participants (40%) became symmetrical (S6, S7, S8), 1 became asymmetrical (S4), 1 showed an increase (S3), and the remaining participant (S1) showed a decrease in values for step length asymmetry over time. Moreover, over time, all the participants maintained the same swing time and step length asymmetry directions as were measured at V1.

Trivial to small ES was observed in walking speed and the spatiotemporal measures on the paretic and non-paretic sides between visits (values ranging from 0.00 to 0.21). However, while swing time symmetry ratio showed poor ES (0.05), the step length symmetry ratio presented with medium power (0.42).

Table 6-2: Walking speed and spatiotemporal parameters

Participant No.	1		2		3		4		5		6		7		8		9		Overall		P value	ES (95% CI)
	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2		
Walking speed (m/s)	0.69	0.44	0.88	1.05	0.86	0.82	0.37	0.44	1.10	1.14	0.75	0.83	0.82	0.9	0.49	0.73	1.18	1.27	0.79(0.3)	0.85(0.3)	.276	0.20(-0.73-1.13)
Swing time symmetry																						
Paretic	0.46	0.61	0.40	0.41	0.53	0.53	0.55	0.50	0.41	0.42	0.60	0.59	0.45	0.45	0.61	0.57		0.46	0.50(0.08)	0.50(0.07)	.790	0.00(-0.92-0.92)
Non-paretic	0.32	0.44	0.34	0.38	0.39	0.38	0.34	0.30	0.39	0.38	0.47	0.44	0.35	0.34	0.53	0.47	0.47	0.48	0.40(0.07)	0.40(0.06)	.870	0.00(-0.92-0.92)
Ratio	1.42	1.39	1.18	1.08	1.37	1.36	1.62	1.67	1.07	1.11	1.28	1.34	1.28	1.32	1.16	1.21	1.01	1.04	1.27(0.19)	1.28(0.19)	.454	0.05(-0.87-0.97)
Step length symmetry																						
Paretic	0.47	0.35	0.45	0.53	0.59	0.56	0.27	0.35	0.61	0.62	0.55	0.60	0.53	0.52	0.43	0.52	0.75	0.78	0.52(0.13)	0.54(0.13)	.370	0.15(-0.78-1.08)
Non-Paretic	0.32	0.30	0.45	0.54	0.50	0.45	0.28	0.28	0.57	0.58	0.61	0.62	0.40	0.48	0.36	0.50	0.70	0.74	0.47(0.14)	0.50(0.15)	.140	0.21(-0.72-1.14)
Ratio	1.45	1.17	1.00	1.02	1.17	1.24	1.05	1.25	1.07	1.07	1.09	1.03	1.31	1.08	1.22	1.04	1.06	1.05	1.16(0.14)	1.11(0.09)	.340	0.42(-0.51-1.35)

Abbreviations: V: Visit; ES: effect size; (m/s); meter/second.

6.3.3 Kinetic Data

Mean V1 and V2 values for knee joint moment amongst the stroke survivors (peak KAM, KAM impulse and peak KFM) are summarised in Table 6-3.

6.3.3.1 Peak KAM

At the initial measurement, peak KAM on the paretic side ranged from 0.12-0.49 Nm/kg (mean 0.29±0.13), and on the non-paretic side, it ranged from 0.08-0.42 Nm/kg (mean 0.26±0.12).

After the (two-year) follow-up, peak KAM was increased in most of the stroke survivors on the paretic (mean 0.41±0.19 Nm/kg, range: 0.21-0.75 Nm/kg) and non-paretic (mean 0.33±0.13 Nm/kg, range: 0.06-0.48 Nm/kg) sides, except on the paretic side in participant S7 and the non-paretic side in participant S4. In addition, while the stroke survivors showed an increase in peak KAM on both sides over time, the non-paretic side moment was significantly different ($f(1,8)=-3.45$, $p=0.008$, ES=0.56), compared to V1. Participants S1, S2, S3, S4 and S6 showed a remarkable increase in peak KAM on the paretic side: by 525%, 27%, 27%, 66% and 22%, respectively. Moreover, peak KAM on the non-paretic side had increased over time in participants S1, S3, S7 and S8, namely by 85%, 37%, 81% and 50%, respectively.

6.3.3.2 KAM Impulse

At the initial measurement, KAM impulse on the paretic side ranged from 0.03-0.28 Nm/kg*s (mean 0.11±0.08) and on the non-paretic side, it ranged from 0.05-0.21 Nm/kg*s (mean 0.11±0.07).

At follow-up, KAM impulse was increased in 7 out of the 9 stroke survivors on the paretic side (mean 0.16±0.11 Nm/kg*s, range: 0.06-0.33 Nm/kg*s) and 5 out of 9 of the participants on the non-paretic side (mean 0.14±0.07 Nm/kg*s, range: 0.06-0.33 Nm/kg*s). However, the change in KAM impulse on either side was not significantly different over time. Moreover,

despite the minor changes in KAM impulse on each side over time, participant S1 showed a remarkable increase of 1000% on the paretic side, compared to V1.

6.3.3.3 Peak KFM

At V1, peak KFM on the paretic side ranged from 0.11-0.91 Nm/kg (mean 0.44±0.28) and on the non-paretic side, 0.14-0.92 Nm/kg (mean 0.50±0.25).

After follow-up (at V2), peak KFM on the paretic side had increased in 4 and decreased in 5 of the 9 participants (mean 0.39±0.26 Nm/kg, range: 0.13-0.92 Nm/kg). While 1 participant (S8) showed a remarkable increase in KFM of 84%, 2 of the participants (S2, S9) showed a remarkable decrease in KFM of 44% and 37%, respectively. In contrast, peak KFM on the non-paretic side was increased in 3 of the participants, decreased in 5 of the participants, and remained stable in 1 participant (mean 0.40±0.14 Nm/kg, range: 0.24-0.59 Nm/kg).

Peak KFM magnitude on both sides amongst the stroke survivors at the initial measurement (V1) demonstrated high inter-subject variability. However, while the variability of peak KFM on the paretic side remained high, the non-paretic side was found to have decreased by 44% over time (by V2).

Small to medium ES was observed in knee joint moments on the paretic side in the stroke survivors between visits (value ranging from 0.43 to 0.75), except for KFM on the paretic side, which displayed a trivial ES (0.19).

Table 6-3: Knee joint moments

Participant No.	1		2		3		4		5		6		7		8		9		Overall		P value	ES (95% CI)
	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2		
Peak KAM (Nm/kg)																						
Paretic	0.12	0.75	0.26	0.33	0.44	0.56	0.15	0.25	0.37	0.40	0.49	0.60	0.22	0.21	0.19	0.23	0.34	0.36	0.29(0.13)	0.41(0.19)	.095	0.30(-0.63-1.23)
Non-Paretic	0.14	0.26	0.23	0.26	0.35	0.48	0.08	0.06	0.35	0.41	0.37	0.39	0.16	0.29	0.26	0.39	0.42	0.44	0.26(0.12)	0.33(0.13)	.008	0.01(-0.91-0.93)
KAM Impulse (Nm/kg*s)																						
Paretic	0.03	0.33	0.06	0.08	0.16	0.20	0.06	0.07	0.09	0.11	0.28	0.32	0.03	0.06	0.14	0.11	0.14	0.13	0.11(0.08)	0.16(0.11)	.191	0.76(-0.20-1.72)
Non-Paretic	0.06	0.13	0.05	0.04	0.19	0.25	0.05	0.03	0.11	0.14	0.21	0.20	0.04	0.11	0.13	0.16	0.19	0.18	0.11(0.07)	0.14(0.07)	.095	0.50(-0.44-1.44)
Peak KFM (Nm/kg)																						
Paretic	0.11	0.13	0.64	0.36	0.17	0.14	0.22	0.15	0.91	0.92	0.44	0.34	0.38	0.41	0.32	0.59	0.78	0.49	0.44(0.28)	0.39(0.26)	.397	0.03(-0.89-0.95)
Non-Paretic	0.22	0.24	0.62	0.36	0.59	0.59	0.26	0.29	0.71	0.33	0.46	0.42	0.57	0.24	0.14	0.52	0.92	0.58	0.50(0.25)	0.40(0.14)	.259	0.23(-0.70-1.16)

Abbreviations: V: Visit; ES: effect size; (Nm/Kg); Newtown-meter/Kilogram; (s): second; KAM: Knee Adduction Moment; KFM: Knee Flexion Moment.

6.3.4 Kinematic Data

The stroke survivors' kinematic data (pelvic obliquity, knee flexion and toe-out parameters), as observed at initial measurement and over time, are presented in Table 6-4.

6.3.4.1 Pelvic Obliquity

At initial measurement (V1), the angle of pelvic obliquity on the paretic side at peak KAM ranged from -2.6°- 6.3° (mean 1.4°±3.5), as 5 out of the 9 participants presented with pelvic hiking. In contrast, the angle of pelvic obliquity on the non-paretic side ranged from -7.7°-2.2° (mean -2.1 ± 2.6), as 8 out of the 9 participants presented with pelvic drop.

Over the two-year follow-up period (by V2), the overall angle of pelvic obliquity on the paretic side decreased by 1.24°, compared to V1 (mean 0.16°±4.6, range: -5.1 - 7.6°), as 4 out of the 9 participants presented with pelvic hiking. In contrast, the overall angle of pelvic obliquity on the non-paretic side showed marginal change, compared to V1 (mean -2.10°±4.23, range: -5.1°-7.6°), since 6 out of the 9 participants presented with pelvic drop.

6.3.4.2 Knee Flexion

At the initial measurement (V1), the peak angle of knee flexion on the paretic side ranged from 28.3°-48.7° (mean 37.4°±8.0), and on the non-paretic side, from 34.8°-62.9° (mean 50.5°±9.5).

By the two-year follow-up (at V2), the peak angle of knee flexion on the paretic side in the stroke survivors had decreased in 6 and increased in 3 of the 9 participants. However, the overall angle of knee flexion on the paretic side had decreased by 7.9°, compared to V1 (mean 29.9°±11.4, range: 11.9°-41.3°) ($f(1, 8)=1.69$, $p=0.12$, ES=0.50). In contrast, the peak angle of knee flexion on the non-paretic side had increased in 2 of the participants and decreased in 7. The overall angle of knee flexion on the non-paretic side was significantly decreased by 4.6°, compared to V1 (mean 45.5°±8.9, range: 34.2°-59.5°) ($f(1,8)=3.13$, $p=0.01$).

6.3.4.3 Toe-out

In the initial measurement (V1), the peak angle of foot progression on the paretic side ranged from -23.5°-34.4° (mean 10.7°±15.0), as 8 out of the 9 participants presented with 'toe-out' (the remaining participant presenting with 'toe-in'). In contrast, the peak angle of foot progression on the non-paretic side ranged from 3.7°-22.3° (mean 17.0±6.7), as all the participants presented with toe-out.

By the end of the two-year period (by V2), the overall angle of foot progression on the paretic side showed marginal change, compared to V1 (mean 10.3°±14.4, range: -22.8-28.4°), as the angle had increased in 4 of the participants and decreased in 5. In contrast, the overall angle of foot progression on the non-paretic side had decreased by 1.7°, compared to V1 (mean 15.3°± 8.0, range: 4.8°-22.9°), with the angle increasing in 3 of the participants and decreasing in 6.

Variation in ES was observed between visits in the stroke survivors' kinematic measures. While the pelvic and toe-out angles showed trivial to small ES (value ranging from 0.01 to 0.30), knee RoM presented with small to medium ES (value ranging from 0.50 to 0.76).

Table 6-4: Kinematic data (In degree) - negative values denoted as pelvic drop for pelvic obliquity and toe-in for foot progression (toe-out) angles

Participant No.	1		2		3		4		5		6		7		8		9		Overall		P value	ES (95% CI)
	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2		
Pelvic obliquity angle (at time of peak KAM)																						
Paretic	3.9	2.3	6.2	-1.7	0.7	2.4	2.5	5.4	-2.2	-5.1	6.3	7.6	-1.9	-0.8	-0.6	-5.5	-2.6	-3.1	1.40(3.5)	0.16(4.6)	.336	0.74(-0.22-1.70)
Non-Paretic	-3.1	0.1	-7.7	-3.2	-2.5	-7.9	-1.9	-7.4	-1.2	-0.9	-2.9	0.8	-0.4	-1.9	2.2	5.7	-1.6	-4.2	-2.13(2.6)	-2.10(4.23)	.986	0.56(-0.38-1.50)
Knee flexion																						
Paretic	48.7	11.9	46.6	41.3	43.6	31.9	30.6	15.7	35.6	40.0	28.4	19.3	28.3	30.9	32.2	39.0	42.2	38.7	37.4(8.0)	29.9(11.4)	.129	0.52(-0.42-1.46)
Non-Paretic	45.3	43.3	47.4	43.9	59.5	51.4	62.9	55.4	57.5	59.5	44.9	37.7	58.9	51.2	34.8	36.8	43.3	34.2	50.5(9.5)	45.9(8.9)	.014	0.43(-0.50-1.36)
Toe-out															-	-						
Paretic	15.8	16.2	12.3	6.6	8.1	13.0	8.6	14.7	34.4	28.4	14.8	10.9	14.4	21.3	23.5	22.8	11.5	4.9	10.7(15.0)	10.3(14.4)	.842	0.19(-0.74-1.12)
Non-Paretic	15.9	21.3	21.9	21.0	15.7	15.0	3.7	0.7	22.1	22.9	20.1	13.2	22.3	22.6	22.0	16.1	9.0	4.8	17.0(6.7)	15.3(8.0)	.225	0.49(-0.45-1.43)

Abbreviations: V: Visit; ES: effect size; KAM: Knee Adduction Moment.

6.4 Discussion

To the present author's knowledge, this case series is the first study to characterise stroke survivors' knee joint load/moment during walking, over a two-year period. The findings from this study provide evidence that knee joint moment changes over time, as KAM (peak and impulse) increases and KFM decreases on both sides. However, the stroke survivors studied here demonstrated high inter-subject variability in KFM over the years following a stroke (some with an increase, and others with a decrease in moment on the paretic and non-paretic sides). This is important, because with increasing age and following a stroke, identifying the long-term biomechanical mechanism/changes underlying stroke-related gait patterns help improve the efficacy and success of rehabilitation strategies after injury. Moreover, it helps gain a better understanding of knee joint loading and how this change that takes place over the years following stroke can help clinicians prioritise gait rehabilitation goals (for example, improving symmetry during walking), in order to limit potential long-term knee joint Musculoskeletal (MSK) problems.

6.4.1 Changes in Knee Joint Moment over Time

This current study demonstrated that mean KAM (peak and impulse) increased on both the paretic and non-paretic sides over time, compared to an initial assessment (in this case, V1), while KAM asymmetry between sides increases. In addition, this change in mean KAM between visits was above the reported SEM value of the measure reported in section 3.8 (less than 3.7%). At a two-year follow-up, mean peak KAM on the paretic and non-paretic sides was found to have increased by 41.4% and 27%, respectively, compared to V1 (significantly different on the non-paretic side; see Table 6-3). In fact, mean peak KAM on the paretic side remained higher in most of the stroke survivors over time, compared to the non-paretic side. However, while previous work by Marrocco et al. (2016) failed to compare the paretic and non-paretic sides statistically, 7 out of the 9 stroke survivors in the above study also demonstrated higher peak KAM on the paretic side, thereby supporting the findings of this current study.

In addition, the increase in cumulative load/moment on the paretic side over time may contribute to a predisposition to knee OA. In the only single radiographic study to be conducted on a stroke survivor, the femoral cartilage on the paretic side was reported to be

reduced in thickness (Tunc et al., 2012). This may have been due to the reduction/absence of mechanical load on the paretic side (Yilmaz et al., 2016); anticipated to cause at least some degree of structural and/or functional atrophy in the articular cartilage (Owman et al., 2014; Souza et al., 2012). With increasing age, it suggests a possible interaction between increased load and a hypothetical decrease in cartilage thickness as part of the pathogenesis of early-onset knee OA in long-term stroke survivors (Andriacchi et al., 2015). However, while there does not appear to be any previous study that has identified a specific threshold beyond which the magnitude of joint moment becomes harmful, the lack of a control group in the above study is one of its limitations. Moreover, there were no radiographic knee joint findings for the stroke survivors over time and so a longitudinal study is warranted, using radiographic or MRI evidence.

In contrast, one reason why the participants in this present study may have failed to report knee pain is their low level of physical activity. In addition to deleterious joint moments, the development of degenerative joint conditions also depends on the cumulative effects of loading (Maly et al., 2013). Furthermore, it is possible that the stroke survivors did not experience knee pain, because compensatory gait may have reduced their knee joint moments. However, previous studies have indicated that stroke survivors report more knee pain over time (Hettiarachchi et al., 2011; Patterson and Sibley, 2016), although compensatory gait patterns were not measured in such studies. Therefore, in the stroke survivors who did not develop any pain, this may have been due to functional compensatory gait patterns; compared to those with knee pain, who may not have developed such gait patterns. While this suggests that compensatory patterns can, in addition to functional gains, afford some management of knee loading in certain individuals, compensatory patterns have also been associated with other deleterious side effects (for example, mechanical and metabolic inefficiency) (Nüesch et al., 2016). Accordingly, future studies should examine joint loading patterns longitudinally in sub-groups of chronic stroke survivors, both with and without knee pain.

In contrast to KAM, the results of this present study indicated that over time, mean KFM on the paretic and non-paretic sides decreased by 11.3% and 20%, respectively, compared to V1 (Increased in 2 and decreased in 5 participants), while KFM asymmetry was found to diminish between sides (see Table 6-3). This change in mean KFM between visits was above the

reported SEM value (less than 8.7%), reported in section 3.8. However, KFM exhibited greater variability over time on the paretic and non-paretic sides (with some participants displaying an increase or decrease and others exhibiting no change in moment on the paretic or non-paretic side). This finding is consistent with previous studies, which indicate high variability in knee joint moment amongst stroke survivors (Marrocco et al., 2016). In addition to the heterogeneity of individuals after stroke, their high variability may therefore be attributed to compensatory gait patterns, which could be responsible for the wide variation in functional and biomechanical changes/gains over a long-term recovery period (Buurke et al., 2008; B. Raja et al., 2012). For instance, factors such as walking speed (Kim and Eng, 2004; Robbins and Maly, 2009) altered knee joint RoM (Chen et al., 2005; Creaby et al., 2013; Farrokhi et al., 2015; Kim and Eng, 2004; B. Raja et al., 2012), and muscle co-activation (Chen et al., 2005; Chiba et al., 2016; Dunphy et al., 2016; Linley et al., 2010; Stanhope et al., 2014) are known to contribute to changes in knee joint moment during walking. Therefore, in future investigations of stroke survivors, longer-term assessments should be considered, in order to evaluate alterations in knee moment with any change in gait pattern.

A longitudinal reduction in KFM among the stroke survivors, especially on the non-paretic side, may have also reduced the possibility of experiencing pain, due to improvements in knee RoM (significantly reduced by five degrees to the level observed at V1) by the two-year follow up. Excessive knee flexion RoM during stance increases KFM and then increases the contact force on the anterior knee compartment (Ho et al., 2012). Therefore, recovery in stroke participants' knee RoM may help reduce the potential risk of patellofemoral knee pain.

6.4.2 Knee Joint Moment and Biomechanical Changes over Time

Understanding the effect of long-term biomechanical changes on knee joint moment/load in stroke survivors is potentially meaningful, if further comorbidities are to be avoided, such as MSK problems. Of the biomechanical variables in this longitudinal study, the potential associated changes in knee joint moment amongst stroke survivors are discussed in relation to longitudinal changes in spatiotemporal and kinematic variables.

6.4.2.1 Walking Speed and Spatiotemporal Asymmetry

In this current study, mean walking speed increased by 7% compared to V1, with walking speed increasing in 66.7% of the stroke survivors (above the reported SEM value of the measure reported in section 3.8 [less than 4.7%]). The current finding for walking speed is in line with the results of a previous study by Patterson et al. (2014), which showed an increase in walking speed over time. Previous studies have reported that walking speed influences knee joint mechanics, such as joint moments (Telfer et al., 2017). In this current study, while 89% of the stroke survivors (8 out of 9 participants) showed an increase in peak KAM on the paretic and non-paretic sides, 5 participants (62.5%) also displayed an increase in walking speed on each side. This result is consistent with those of a previous study, which showed a link between increased walking speed and increased peak KAM (Telfer et al., 2017). An Increase in walking speed was also reported to increase GRF, followed by peak KAM (Robbins and Maly, 2009; Telfer et al., 2017).

In contrast to peak KAM, however, walking speed was reported to be inversely related to KAM impulse, with an increase in walking speed producing lower KAM impulse (Robbins and Maly, 2009). Nevertheless, although more than 50% of the stroke survivors in this current study (7 participants on the paretic side and 5 on the non-paretic side) presented with increased KAM impulse over time, 4 participants displayed increased walking speed on the paretic side and 2 participants, on the non-paretic side. This result is inconsistent with Robbins and Maly (2009) findings for a healthy population, which can be explained by 1) an increase in peak KAM magnitude in most the stroke survivors (8 out of 9), as part of a KAM impulse waveform, and 2) the stroke survivors' gait being associated with numerous compensatory mechanisms compared to a healthy population, which could have played an important role in altering knee joint moment (Chen et al., 2005; Chiba et al., 2016; Dunphy et al., 2016; Linley et al., 2010; Stanhope et al., 2014a).

The change in walking speed on the sagittal plane alters KFM, because of the remarkable effect of speed on joint motion on the sagittal plane and lever arm (van den Noort et al. (2013)). Accordingly, KFM moment increases with the acceleration of walking speed. In addition, reduced walking speed results in reduced KFM. In the current study, while walking speed was found to increase in most of the stroke survivors over time, KFM increased in only 2 participants on the paretic side and 2 on the non-paretic side. In contrast, 5 participants

showed decreased KFM on the paretic side, as did 4 participants on the non-paretic side. This inconsistency in the previous literature may be attributed to impaired knee joint motion, caused by compensatory strategies, spasticity, weakness, impaired sensory-motor control and/or muscle weakness (see Table 6-1 and Table 6-4) (Jonkers et al., 2009; Lee et al., 2015; B. Raja et al., 2012). This may also explain the increase in KFM variability in stroke survivors, which was found in this current study.

At a two-year follow-up, the mean change in temporal and spatial asymmetry was comparable to V1. However, in an analysis of the stroke survivors, the data revealed that over time, swing time asymmetry had increased in 5 of the participants (55.6%; all with longer swing time on the paretic side), while step length asymmetry had decreased in 4 of the participants (44.4%; all with longer paretic side step length). Any changes in spatiotemporal asymmetry were based on the SEM value reported in section 3.8. (less than 2.4% for temporal symmetry and less than 2.9% for spatial symmetry). However, these current findings for spatiotemporal asymmetry are inconsistent with those of a previous longitudinal study by Patterson et al. (2014), where no change in spatiotemporal asymmetry was reported in the majority of the stroke survivors over a two-year period. This inconsistency is possibly due to 1) a lack of specific training on the in-patient rehabilitation programme for spatiotemporal asymmetry in the previous study, and 2) varying periods of time having elapsed since the onset of stroke at initial measurement in this current study (an average of 86.3 months), compared to the previous work (average 19.7 days).

It was hypothesised that increasing the swing time asymmetry ratio, with consistently longer periods of time spent in non-paretic stance, would increase GRF and subsequently, knee KAM on the non-paretic side (Kim and Eng, 2003; K. K. Patterson et al., 2008). Contrary to this hypothesis, KAM (peak and impulse) was found to increase on both sides in the stroke survivors in this current study (4 participants for each side), with an increase in swing time asymmetry. This variability in KAM within and between the participants supports Marrocco et al. (2016) results, where high KAM variability was indicated amongst stroke survivors. In contrast, except for 2 participants for each side (paretic and non-paretic), an increased swing time asymmetry ratio did not reveal a causal link with increased KFM in stroke survivors. However, KFM was reduced on the paretic side in 4 participants and on the non-paretic side in 5 participants, but with no evidence of changes in swing time symmetry ratio over time.

However, the discrepancy in KAM and KFM findings, with swing time asymmetry ratio, may be attributed to the small sample size and the various compensatory strategies proposed to alter joint mechanics (Kim and Eng, 2003; Marrocco et al., 2016).

Amongst the stroke survivors (88.9%) who showed an increase in KAM over time, only a few exhibited changes in KAM (2 increased and 1 decreased), with a change in step length asymmetry. However, while step length asymmetry was reported to have a causal effect on KFM, increasing it on the non-paretic side in stroke survivors (Allen et al., 2011), the participants' KFM in this current study presented high variability (within and between individuals), with changes in step length asymmetry over time. This is most likely due to the small sample size in the present study, which contributed to the observed variability in knee joint moment patterns. Therefore, a large sample size is needed in a future study to enable a conclusion to be drawn.

6.4.2.2 Kinematic Changes

Pelvic obliquity is an important indicator of the compensatory pattern that is commonly observed in stroke survivors during walking (Stanhope et al., 2014b). Evidence from previous studies has pointed to a relationship between pelvic movement pattern and frontal plane moment (KAM measures) (Dunphy et al., 2016; Takacs and Hunt, 2012). In this current study, pelvic obliquity on the paretic side was found to be reduced (dropped) by 88.5% over time, compared to V1, while the non-paretic side was comparable to V1. Amongst the stroke survivors who displayed increased KAM on the paretic side (peak and impulse), pelvic obliquity was found to have decreased (dropped) on the non-paretic side in 3 participants (37.5%); meanwhile, 3 participants (43%) exhibited increased peak KAM and 3 displayed increased KAM impulse over time. Similarly, amongst the stroke survivors with increased KAM on the non-paretic side (peak and Impulse), pelvic obliquity on the paretic side was found to have decreased (dropped) in 4 participants (50%), in whom peak KAM had increased, and 2 participants (40%), in whom KAM impulse had increased over time. This finding illustrates the influence of pelvic drop on frontal plane moment in the knee amongst stroke survivors, which is consistent with previous work on healthy populations (Dunphy et al., 2016; Takacs and Hunt, 2012). However, contrary to previous studies (Chiba et al., 2016; Linley et al., 2010), very few of the stroke survivors with increased pelvic obliquity (tilt) demonstrated

any change in KAM on either side. This may be attributed to the pattern of lateral movement in the trunk, which was found to alter knee joint moments during walking (Bechard et al., 2012; Gerbrands et al., 2017; Takacs and Hunt, 2012). Therefore, trunk moment pattern should be considered for future study.

Knee joint moment on the sagittal plane (KFM) is associated with altered knee joint flexion patterns (Creaby et al., 2013; Ho et al., 2012). Accordingly, increased knee flexion RoM increases KFM and knee load (Ho et al., 2012). Post-stroke knee RoM is influenced by many factors such as compensatory strategies, spasticity, weakness, impaired sensory-motor control and/or muscle weakness (Jonkers et al., 2009; Raja et al., 2012; Lee et al., 2015). In this current study, knee RoM decreased on the paretic and non-paretic sides over time, compared to V1 (significantly decreased on the non-paretic side). Mean KFM on the paretic side decreased in 6 and increased in 3 of the participants. Out of the reduced KFM on the paretic side in the stroke survivors, 4 participants (66.7%) displayed decreased knee RoM, while out of those who exhibited increased KFM, 1 participant (33.3%) showed increased KFM. However, compared to the paretic side, mean KFM on the non-paretic side was found to have decreased in 7 participants and increased in 1 participant. Amongst the stroke survivors with reduced KFM on the non-paretic side, 3 participants (42.8%) displayed reduced knee RoM. Taking all the KFM results together, most of the reduction in KFM amongst the stroke survivors may have been influenced by their reduced knee RoM. Surprisingly, most of the stroke survivors (75%) who presented with increased KAM, showed reduced knee RoM over time.

Theoretically, knee joint RoM plays an important role in shock absorption during stance. Accordingly, increased stiffness of knee joint RoM and reduced RoM excursion have a major influence on GRF and therefore, on changes in the magnitude of moments (Zeni and Higginson, 2009). Post-stroke impairments such as increased muscle tone, muscle co-activation, and muscle weakness have been found to increase joint stiffness (Heiden et al., 2009). Therefore, increased KAM magnitude may explain what has been proposed in previous studies, concerning the association between reduced knee RoM and increased joint moment.

Foot progression, whether toe-out or toe-in, is found to have an effect on lower limb joint load (KAM measures) (van den Noort et al., 2013). However, the relationship between KAM

measures and foot progression direction (toe-out or toe-in) is still found to vary in the literature (Simic et al., 2013). In the current study, mean foot progression on the paretic and non-paretic sides overtime was comparable to V1. However, despite increased KAM in most of the participants, the foot progression results indicated high variability within and between participants. In fact, residual impairment and spasticity (see Table 6-1) may play an important role in the different foot movement patterns observed during walking (Roche et al., 2015). This could make it difficult to draw any conclusion regarding the effect of foot progression changes on KAM measure.

6.5 Future Work

Future studies are required to examine joint loading patterns longitudinally in acute-stroke sub-groups, both with and without knee pain. Given that rehabilitation goals often aim to remedy compensatory gait patterns and restore more normative kinematics and kinetics, it is important to understand the nature of knee joint moment in the context of long-term biomechanical and functional recovery. In short, the link between stroke survivors' compensatory mechanisms and biomechanical changes during walking, and altered knee joint moments, need to be studied.

6.6 Limitations of the Study

The primary limitation of this case series is the absence of a comparison (control) group. A control group is a group of healthy individuals, who match an intervention or specifically sampled group (here, the stroke survivors), in terms of mean age and walking speed. Another limitation of this study was that physical activity was not assessed, which could have provided important additional insights into the occurrence of repeatedly high joint moments, experienced by stroke survivors in daily life. In this current study, the small sample size represents a further limitation, as it did not enable the detection of clinically relevant differences between visits. Finally, another limitation was the absence of radiographic evidence for the stroke participants; leaving open the possibility that some structural changes in the knee joint may have already been present in the group.

6.7 Conclusion

Over time, knee joint moment changes in stroke survivors, as KAM increases and KFM decreases. However, KFM showed high variability within and between stroke survivors. Increased walking speed and pelvic drop indicated that joint moments in the frontal plane and compensatory gait patterns can change over the years following stroke. While reduced knee joint RoM also reduced KFM, the majority of the stroke survivors with increased KAM also displayed reduced knee joint RoM over time. In its pathology, stroke leads to major impairments and deformity, which interfere with these firmly regulated patterns. Hence, compensatory mechanisms can develop to maintain proper gait function. Although previous studies have investigated the influence of a few mechanical changes on knee joint load, stroke survivors present with numerous gait abnormalities and compensations over time, which may in turn manipulate joint load (moment) in various ways. Future longitudinal studies are therefore necessary to examine joint loading patterns, together with their association with compensatory gait patterns and levels of physical activity; from the earliest post-stroke stages and in sub-groups of individuals with chronic stroke, both with and without knee pain.

Chapter 7: General Discussion and Conclusion

7.1 Introduction to Discussion

Asymmetrical gait is a characteristic and persistent post-stroke impairment that is associated with many deleterious consequences, such as mechanical and metabolic inefficiencies. It has also long been hypothesised to increase the risk of developing joint wear and tear and OA (Patterson et al., 2014). However, aside from one recent survey study that highlights an increase in comorbid arthritis in a sample of stroke survivors (Patterson and Sibley, 2016), there has been no research to directly test the hypothesis that asymmetrical gait leads to increased joint wear and tear.

Following stroke, altered gait mechanics constitute just one factor of the potential risk of developing knee joint OA. Other risk factors of knee OA shared by stroke survivors include age, high BMI and altered gait mechanics (Marini et al., 2001; Sheffler et al., 2014). Persistent post-stroke alterations to gait pattern may play a role as mechanical stimuli, provoking biological processes that underlie the development of OA (Andriacchi et al., 2015). With steady improvement in long-term survival after stroke (Boysen et al., 2009), stroke survivors subsequently face a greater number of years of cumulative exposure to changes of a biomechanical (spatiotemporal symmetry, kinematics and kinetics) and biological (increased age and BMI) nature, which may mean that their knee joints become less capable of adapting to excessive or repetitive loading, thus leading to knee OA.

Despite the many possible stroke-related biomechanical changes (in the context of biological susceptibility), which contribute to the development of knee OA, there is a lack of studies that characterise knee joint moments (reflecting loading) in stroke survivors. Therefore, the main contribution of this thesis to the pool of relevant knowledge is a better understanding of the nature of stroke survivors' knee joint load; exploring the potential risk of knee OA and establishing the influence of key biomechanical factors on knee joint moments. Accordingly, this thesis is the first work to directly characterise knee joint moments in a cohort of stroke survivors and to do so over time (assessed on two different occasions: at baseline and at a two-year follow-up). Where there is a high degree of asymmetry in knee joint moments, between limbs and joint moments in otherwise healthy adults, there is greater risk of

developing OA. Therefore, in order to achieve the overall research aim, the objectives of this project were set out as follows:

1. To explore the difference in knee joint moments between the paretic and non-paretic sides in stroke survivors. Interlimb differences in stroke survivors' knee joint moments may reveal factors that contribute to increased or adversely shifted joint loading as a consequence of asymmetric gait pattern.
2. To explore the difference in knee joint moments between the paretic and non-paretic sides in severe and less severe spatiotemporal (swing time and step length) asymmetry subgroups. Given that gait after stroke is commonly characterised by spatiotemporal asymmetry, the severity of this asymmetry may indicate a biomechanical mechanism underpinning altered knee joint load and the development of comorbid OA in stroke survivors, as reported in other populations (those with pathological gait).
3. To explore the difference in knee joint moments between stroke survivors and healthy adults, walking at both SS and slow speeds (matched to the stroke survivors). The finding that knee joint moment in stroke survivors exceeds that of healthy controls may indicate a risk of joint OA. Factors like walking speed play an important role in altering knee joint moments. Accordingly, walking speed was considered here (as a confounding effect) in the comparison between groups.
4. To explore the difference between paretic and non-paretic sides in severe and less severe asymmetry subgroups and healthy participants, with regard to the limbs while walking; with the healthy participants walking at SS and slow speeds (matched to the stroke survivors).
5. To explore the immediate effect of imposing symmetrical gait pattern (based on spatiotemporal symmetry) on knee joint moments in stroke survivors. Restoring stroke survivors' walking symmetry is one of the main aims of rehabilitation after stroke. However, it is not known to what extent promoting symmetrical gait patterns in stroke survivors affects knee joint load.
6. To take initial and then repeat measurements (at a two-year follow-up) of knee joint moments in stroke survivors. Due to the fact that stroke survivors have greater life expectancy following stroke nowadays, they potentially face more years of cumulative

exposure to biomechanical and biological changes. This could mean that their knee joints become less adaptable to excessive or repetitive loading, thereby leading to knee OA.

This current work therefore sheds new light on how each factor that influences knee joint moment is altered after stroke and these are discussed in turn.

7.2 Walking Speed

In healthy individuals, knee joint moments (peak and impulse) are affected by a change in walking speed. The results of this study showed that a reduction in walking speed (from SS to 0.8 m/s) in healthy controls decreases peak KAM and KFM by 13% and 50%, respectively. Moreover, a reduction in walking speed increased KAM impulse by 33.3%. However, although stroke survivors walk far more slowly than healthy individuals, their knee joint load does not respond in a similar manner to that of healthy individuals, walking at an equally slow speed. Accordingly, the results for the cohort **(see Chapter 4)** showed that peak KAM and KAM impulse in the stroke survivors were lower than in the healthy participants, walking at the (matched) speed of 0.8 m/s, whereas peak KFM in the stroke survivors was higher on both sides (significantly so on the non-paretic side) (see Figure 4-1 and Figure 4-2). Longitudinally, the majority (89%) of the stroke survivors who displayed an increase in peak KAM on the paretic and non-paretic sides over a two-year period presented with an increase in walking speed **(see Chapter 6).** This reverse effect of slow walking speed on peak KAM in the stroke survivors, compared to healthy subjects, may be attributed to other compensatory gait patterns after stroke, which influence or modify the effects of speed on joint moments. Similarly, the presence of compensatory mechanisms (for example, increased RoM) may also be responsible for increasing KFM on the non-paretic side, thereby increasing the risk of patellofemoral pain and joint degeneration (Creaby et al., 2013; Farrokhi et al., 2015; Ho et al., 2012; O'Connell et al., 2016; Teng et al., 2015).

7.3 Spatiotemporal Asymmetry

In this current study, the influence of spatiotemporal (swing time and step length) asymmetry on knee joint moment is presented from the following perspectives: according to the severity of the spatiotemporal asymmetry **(see Chapter 4),** with the imposition of spatiotemporal

symmetry, the imposition of spatiotemporal ***asymmetry*** **(see Chapter 5 for both cases),** and over a two-year period **(see Chapter 6).**

7.3.1 Temporal Asymmetry

According to the knee joint moment results obtained for the stroke survivors, post-stroke swing time asymmetry did not increase knee joint load (KAM and KFM), with knee joint moments not exceeding those of the healthy controls. Despite the significant swing-time asymmetry in most of the stroke survivors (prolonged swing time on the paretic side and prolonged stance time on the non-paretic side), the results of this current study contradict those of previous studies, which widely demonstrate that gait asymmetry increases stance time on the non-paretic side and consequently, loading (Jones et al., 2013; Lloyd et al., 2010). Moreover, the absence of any increase in knee joint moment in the subgroup of stroke survivors with severe swing time asymmetry (**see Chapter 4**), after imposing swing time asymmetry on the temporal symmetry subgroup (**see Chapter 5**) and during swing time symmetry changes over time (**see Chapter 6**) support this contradiction.

It is suggested here that the absence of any difference in KAM (peak and impulse) between sides and compared to healthy individuals is due to the fact that increased pelvic obliquity of the paretic limb (see Table 4-1) counteracts the effects of swing time asymmetry. Specifically, increased pelvic obliquity (tilt) reduces the KAM moment arm (Linley et al., 2010; Chiba et al., 2016), and therefore, the magnitude of peak KAM on the non-paretic side.

In contrast to the results for the stroke survivors' knee joint moment, where there was severe swing time asymmetry, the stroke survivors with less severe swing time asymmetry surprisingly showed higher KFM on the paretic and non-paretic sides, compared to healthy slow walkers (**see Chapter 4**). Increased KFM in the less severe group was most likely due to increased walking speed, which subsequently pointed to increased knee ROM and muscle co-contraction (Allen et al., 2011; Kim and Eng, 2004). However, despite swing time symmetry being imposed on stroke survivors with temporal asymmetry (**see Chapter 5**), the results failed to show true changes in knee joint load. This may be attributed to the resistance of spatiotemporal asymmetry to change (S. L. Patterson et al., 2008). Therefore, since improving gait symmetry is one of the main goals following stroke, intensive walking practice in future

work could help bring about meaningful adaptation to protocol, instead of immediate effects. This would offer satisfactory insights into knee joint load in stroke survivors after imposing improved symmetry.

7.3.2 Spatial Asymmetry

Similar to temporal asymmetry, post-stroke step length asymmetry did not increase knee joint load in the stroke survivors, compared to the healthy controls, even in a subgroup with severe step length asymmetry (**see Chapter 4**). This finding contradicts those of previous studies, which show that KFM increases on the non-paretic side in stroke survivors with a long step length on the paretic side (Allen et al., 2011). The fact that there were no changes in KFM in the current study was likely to be due to the varying direction of step length asymmetry between the stroke survivors. Surprisingly, as reported earlier in the temporal asymmetry section of this thesis, the stroke survivors with less step length asymmetry presented with higher KFM on the paretic and non-paretic sides, compared to healthy controls walking at a slow matched speed. This increased KFM was most likely to be the outcome of faster walking speed in the symmetrical subgroups (see Table 4-1). In addition, similar foot propulsion and GRF on the paretic and non-paretic sides among symmetrical stroke survivors while walking, as proposed by previous studies (Balasubramanian et al., 2007; Kim and Eng, 2004), may reflect increasing KFM, compared to healthy slow walkers. Heightened KFM can in fact develop the risk of patellofemoral joint pain and knee joint degeneration (Teng et al., 2015). However, after imposing step length symmetry on the participants with spatial asymmetry (**see Chapter 5**), no systematic changes in KFM were observed (on either the paretic or non-paretic side), compared to the baseline conditions. This difference in findings may be attributed to the minor improvement in step length symmetry (resisted changes) and small sample size used in the current study (n=5).

7.4 Biomechanical Factors/Compensation

During walking, stroke survivors develop different compensatory or asymmetry strategies in response to the insufficient return of nervous system function, in order to achieve a safe and functional gait pattern (Levin et al., 2009; B. Raja et al., 2012). The variation in joint moment symmetry of the frontal plane (reflected in KAM) between the paretic and non-paretic sides may be related to the pattern of pelvic obliquity movement in stroke survivors. In this study,

asymmetrical pelvic obliquity was observed across all the stroke survivors, whereby the paretic sides tilted, and the non-paretic sides dropped. This resulted in reduced KAM on the non-paretic side, due to a shift in the centre of mass and a consequent reduction in moment arm. As described in Chapter 4, high pelvic tilt on the paretic side may have reduced KAM on the non-paretic side in the cohort of stroke survivors. Although peak KAM on the non-paretic side did not differ significantly from peak KAM on the paretic side, or from the healthy controls, it was lower in magnitude.

Meanwhile, with regard to spatiotemporal asymmetry in the stroke survivors, the greater its severity, the greater the oblique pelvic asymmetry between sides. Consequently, this is most likely to be responsible for the peak KAM asymmetry observed in stroke survivors with severe spatiotemporal asymmetry. Longitudinally, the stroke survivors' pelvic obliquity was found to change over time (decreased by 1° at Visit 2, compared to the initial measurement), reflected in increased peak KAM on the non-paretic side.

Chapter 5 reports that pelvic obliquity remained unchanged (resisted change) after the imposition of spatiotemporal symmetry on stroke survivors with spatiotemporal asymmetry. Accordingly, peak KAM asymmetry between the paretic and non-paretic sides was still present. In contrast, imposing spatiotemporal asymmetry on symmetrical stroke survivors increased pelvic tilt on the long side (long step length and swing time) and this was similar to what was found in the asymmetrical stroke survivors. Such an increase in pelvic tilt may be responsible for reduced peak KAM on the contralateral sides in stroke survivors.

After a stroke, the non-paretic side plays an important role in maximising functional ability through different adaptive compensatory strategies (based on the paretic side's impairments and level of functioning). Increased muscle co-contraction and altered knee RoM, as compensatory strategies, were found to enable the non-paretic side to attain stability and better functioning (Heiden et al., 2009). However, the consequence of increasing these factors on the non-paretic side was to increase joint moment on the sagittal plane (Allen et al., 2011), potentially leading to an increase in the risk of joint injury (for example, patellofemoral joint pain/OA). In the cohort of stroke survivors (see Chapter 4), a significant increase in KFM on the non-paretic side (compared to healthy controls walking slowly) could be attributed to the increase in knee RoM on the non-paretic side during stance (see

Table 4-1) (Creaby et al., 2013; Ho et al., 2012). Moreover, in addition to increased knee RoM, evidence in the literature strongly suggests that muscle co-contraction on the non-paretic side (as a common impairment/compensation in stroke survivors), was another possible reason for increased KFM on the non-paretic side (Allen et al., 2011; B. Raja et al., 2012). However, a potential limitation of this study was that the method used did not account for muscle co-contraction, which could have helped interpret the findings for knee joint load.

These compensatory mechanisms, combined with an increase in walking speed may also play a role in increasing bilateral KFM in temporal and spatial symmetrical subgroups of stroke survivors (see Chapter 4), compared to a healthy control group walking at a slow speed (Allen et al., 2011, 2014; Balasubramanian et al., 2007; Kim and Eng, 2004; B. Raja et al., 2012). In the longitudinal study (see Chapter 6), the improvement in knee RoM on the non-paretic side over time reduced KFM on the non-paretic side, compared to the initial measurement (decreasing to the healthy control's normal limit, as indicated in Chapter 4). Surprisingly, most of the stroke survivors (75%) who presented with increased KAM displayed reduced knee RoM over time. Theoretically, knee joint RoM plays an important role in shock absorption during stance. Accordingly, increased stiffness in knee joint RoM and reduced RoM excursion have a major influence on GRF and therefore, on changes in the magnitude of moments (Zeni and Higginson, 2009). Post-stroke impairments such as increased muscle tone, muscle co-activation, and muscle weakness have been found to increase joint stiffness (Heiden et al., 2009). Consequently, increased KAM magnitude may explain what has been proposed in previous studies, regarding the association between reduced knee RoM and increased joint moment.

7.5 Potential Risk of Osteoarthritis (OA) in Stroke Survivors

The results of this work show for the first time that knee joint load on the ***frontal plane*** (peak KAM and KAM impulse) is unlikely to increase the ***biomechanical risk factors*** for developing knee joint musculoskeletal injury after a stroke. Although the stroke survivors in this study shared the same risk of developing knee joint OA, such as age, high BMI and altered gait mechanics (for example, spatiotemporal asymmetry), the results of this thesis demonstrate that the stroke survivors' knee joint load (KAM) did not exceed that of the healthy controls. This may be attributed to additional compensatory gait patterns (for example, pelvic obliquity

[tilt]) following a stroke, which produce the side effect of lowering knee joint moment during walking. Slow walking speed may also be one of the fundamental factors that protect stroke survivors' knee joints from an increase in peak KAM and the risk of OA.

However, while the stroke survivors' KAM was lower than that of the healthy controls, one stroke survivor (S5) reported knee joint pain on the non-paretic side (**see Chapter 6**). It was observed that this stroke participant's mean KAM was lower than that of the healthy controls, walking at SS and slow speeds. However, an analysis of the demographic data revealed that this participant was a 70-year old, with 46 years since the onset of stroke. It would therefore suggest that the cumulative effect of post-stroke gait impairments (relying on the non-paretic side while walking) may have had an impact on the internal structures of the knee and consequently, knee joint OA/pain. Accordingly, using an inverse dynamic approach to estimate intersegmental force will not give a comprehensive insight into the force of knee joint contact. Since measuring contact force *in vivo* is extremely difficult, musculoskeletal modelling may be considered as an alternative approach to estimating knee joint contact force, due to the contribution made by individual muscles during walking (Ogaya et al., 2014). Conducting such work as future research would enable further analysis of the magnitude of contact force on stroke survivors' knee joints, particularly on the non-paretic side.

Nevertheless, it is not only mechanical factors that are responsible for knee joint OA in stroke survivors, but also biological factors. Moreover, aside from post-stroke impairments, OA may have occurred in the stroke survivors sampled in this present study, due to the biological changes that generally accompany aging. These changes consist of articular cartilage tissues becoming less able to stimulate repair; reduced stability in the joints; reduced muscle strength, and slow peripheral neurological responses (Greene and Loeser, 2015; Palazzo et al., 2016). Moreover, the changes to cumulative load/moment on the paretic side, which take place over time (**see Chapter 6**) may be partially responsible for a predisposition to knee OA. In one radiographic study on a stroke survivor, representing the only one of its kind in the literature, reduced thickness was reported in the femoral cartilage on the paretic side (Tunc et al., 2012), which may have been the result of a reduction or absence of mechanical load on the paretic side(Yilmaz et al., 2016). This would be expected to cause at least some structural and/or functional atrophy in the articular cartilage (Owman et al., 2014; Souza et al., 2012). With age, a potential interaction between increased load and a hypothetical decrease in

cartilage thickness is suggested as part of the pathogenesis of early-onset knee OA in long-term stroke survivors (Andriacchi et al., 2015). In sum, the stroke survivors in the current study are at an age (mean age 64±13.1 years) where rapid increase in the incidence of knee joint OA are to be anticipated (Jordan et al., 2007; Patterson and Sibley, 2016).

The main stroke-related motor impairments in the stroke survivors sampled in this study had led to reduced physical activity and subsequently, weight gain (increased BMI) (Sheffler et al., 2012). However, stroke survivors BMI remained unchanged over time (**see Chapter 6**), and their high BMI (mean BMI 26±3.8 Kg/m^2) was inconsistent with the findings of previous studies, which indicate that most of stroke survivors are likely to be overweight/obese (Towfighi and Ovbiagele, 2009). Given that an increase in BMI can serve as a potential barrier to long-term, post-stroke motor and functional recovery (Sheffler et al., 2012), previous studies have found stroke survivors with high BMI to be more at risk of developing joint arthritis, compared to those with stroke alone (Patterson and Sibley, 2016). Therefore, body mass management after stroke has often been recommended to avoid triggering/developing musculoskeletal comorbidities, with a BMI of between 18.5 and 25 kg/m^2 being advised for stroke survivors (Scherbakov et al., 2011).

The results of this work highlight that knee joint load (KFM) on the ***sagittal plane*** carries most risk of musculoskeletal injury (patellofemoral pain/OA) to the knee joint in stroke survivors. As reported earlier, stroke survivors' KFM was found to be higher than that of healthy controls, walking at comparable speeds and in two different situations: first, on the non-paretic side in the stroke survivor cohort, and second, on the paretic and non-paretic sides in stroke survivors with less severe spatiotemporal asymmetry. Heightened KFM in stroke survivors is likely to be due to increased non-paretic knee RoM (Creaby et al., 2013), which may be accompanied by increased muscle co-contraction to compensate for reduced function in the paretic side (for example, reduced foot propulsion) (Kim and Eng, 2004; B. Raja et al., 2012). Both increased knee ROM and co-contraction have previously been found to increase contact force at the knee and the potential risk of patellofemoral and tibiofemoral joint pain and degeneration (Farrokhi et al., 2015).

Heightened KFM on the non-paretic side has also previously been reported in stroke survivors (Kim and Eng, 2004; Teixeira-Salmela et al., 2001) and is suggested as being due to asymmetric

step length (Allen et al., 2011). Indeed, the participants in this current study demonstrated high step length asymmetry, but little joint pain, despite an average of five years having elapsed since the onset of stroke. Although previous studies have indicated increased knee pain in stroke survivors over time (Hettiarachchi et al., 2011), reports of pain in the current study did not appear to have changed appreciably by the two-year follow-up. This may be due to the fact that peak KFM on the non-paretic side appeared to have diminished over the two-year period. However, step length asymmetry did not change during this time, calling into question the notion that this was the reason for heightened KFM on the non-paretic side. Moreover, there were no radiographic knee joint findings for the stroke survivors over time and so a longitudinal study is warranted, using radiographic or MRI evidence.

7.6 Future Work

Stroke survivors are potentially at risk of developing secondary complications of the knee joint due to abnormal changes in knee joint load (alongside biological susceptibility), particularly the knee flexor moment. Thus, exploring joint-loading patterns longitudinally in acute stroke subgroups, either with or without knee pain, would help shed more light on the nature of knee joint load in stroke survivors over time. Furthermore, the relationship between the development of post-stroke gait impairments (for example, spasticity, muscle weakness, and poor balance) and increased/decreased knee joint load, need to be explored. The link between stroke survivors' compensatory mechanisms and biomechanical changes during walking (for example, pelvic obliquity, trunk lean, knee joint RoM and foot propulsion) and altered knee joint moments should be studied. Moreover, future work is necessary to determine the relationship between the potential for recovery, due to these compensatory mechanisms (whether occurring naturally or through therapeutic intervention), and changes in knee joint load in stroke survivors.

In this study, the measurement of knee joint load in stroke survivors was performed for just a few individual walking strides, instead of during daily activities. However, articular cartilage response to knee joint load varies, because it takes place in a time-dependent manner (i.e. the longer the exposure to the load, the greater the deformation of the cartilage) (S. M. Robbins et al., 2009). Therefore, measuring cumulative load as future work on stroke

survivors may help to explore their risk of OA, according to the level or duration of their physical activity.

In short, improving walking speed is one of the main targets of post-stroke treatment. Future research is therefore necessary to investigate how knee joint moments change when stroke survivors increase their speed (based on Perry et al.'s 1995 classification of stroke survivors' level of community ambulation). Moreover, the use of inverse dynamic approaches is very important for estimating knee joint load. However, these approaches underestimate knee joint contact force, as it does not account for the compressive force exerted by muscles during walking. Since measuring contact force *in vivo* is extremely difficult, musculoskeletal modelling is considered as an alternative means of estimating contact force in the knee joint, due to the contribution of individual muscles during walking (Ogaya et al., 2014). While muscle co-contraction is common after stroke, conducting such work as future research would help with a further analysis of the magnitude of contact force on stroke survivors' knee joints.

In addition, investigating the effect of imposing spatiotemporal asymmetry/symmetry on knee joint load is required, using a large sample size to enable a deeper understanding to be gained of the effect of gait asymmetry on knee joint moment during walking. Further important future work should involve examining whether intensive walking practice, using an advanced treadmill to impose asymmetrical/symmetrical patterns, can produce a meaningful effect on knee joint load, compared to the immediate effect protocol. This would help yield better insights into effects on stroke survivors' knee joint load after imposing symmetry and controlling and/or organising different walking speeds.

7.7 Clinical Implications

As stroke survivors share the same primary risk factors, namely increasing age and BMI, it is essential for clinicians to be aware of the importance of knee joint load (as a mechanical stimulus) and its consequences, with regard to stroke survivors' risk of developing musculoskeletal injuries. The presence of knee OA in stroke survivors limits the potential for rehabilitation and functional outcomes, as well as increasing length of stay (Doruk, 2013; Nguyen-Oghalai et al., 2005). Therefore, early diagnosis, prevention, and providing proper

interventions for such morbidity may help to avoid any further complications and enhance speed of recovery.

Aside from the above, the longitudinal study results **(see Chapter 6)** suggested that stroke survivors' exhibit small and variable changes to knee joint load over time. Accordingly, it is important to understand the long-term potential for joint degeneration in stroke survivors (at any stage; acute or chronic), occurring due to continued walking with altered gait patterns.

The hypothesis that stroke survivors are likely to have high knee joint load on the non-paretic side is not confirmed by the results of this work. Based on the inverse dynamic approach (mechanical loading), they are not at risk of developing knee OA in the medial compartment of the non-paretic side. In contrast, there is a greater potential risk of patellofemoral pain/OA on the non-paretic side, due to high KFM, compared to healthy controls. However, a deeper understanding of the knee joint contact force that results from muscular co-contraction is necessary for estimating the potential direct contact force on knee joints and true risk of heightened knee joint load (in the context of biological susceptibility).

Using hip and pelvic assessment when dealing with stroke survivors' impairments and physical examinations may help to identify a potential increase/decrease in knee joint load. For example, muscle weakness in hip-abductors can lead to contralateral pelvic drop, which will in turn increase moment arm and KAM on the affected side. In contrast, evaluating pelvic movement pattern (tilt and/or drop) can give a clear impression of the effect of pelvic abnormality on knee joint moment. However, an asymmetrical pelvic obliquity pattern is presented in most stroke survivors and this asymmetry increases with severe spatiotemporal asymmetry.

The imposition of spatiotemporal symmetry is a common practice implemented by clinicians when dealing with asymmetrical stroke survivors (for example, studies have shown that walking to external auditory cues may be helpful in improving gait coordination and temporal asymmetry (Hollands et al., 2016)). However, despite the results of this current study (**see Chapter 5**) showing no effect of imposing symmetry on knee joint load, this effect is still unclear, because of the potential limitations of this study, namely its small sample size and the resistance of spatiotemporal symmetry to change. Therefore, a consideration of these

limitations in future studies would help draw conclusions over the relationship between imposing gait symmetry and altered knee joint load.

Post-stroke compensatory patterns on the non-paretic side (for example, muscle co-contraction and increased knee RoM) appear to serve the purpose of gaining a steady-state walking pattern, as a result of a weak and uncoordinated paretic side (B. Raja et al., 2012). However, these compensatory mechanisms can increase knee joint load and the risk of patellofemoral pain. Thus, improving function on the paretic side and reducing impairments may help to minimise compensatory mechanisms on the unaffected side and consequently, the risk of musculoskeletal injury. Therefore, compensatory gait patterns and their influence on knee joint moment/loading should be considered during rehabilitation.

7.8 Limitations

A limitation of this current study was the absence of any physical activity assessment, which would otherwise have permitted further key insights into the extent of stroke survivors' daily joint load repetition. Moreover, there was no radiographic data available for the subgroups of stroke survivors or healthy controls. This means that there may have been structural changes in the participants' knee joints. As such, the estimated knee joint load and potential risk of OA depended on external knee joint moments (KAM and KFM), as opposed to any structural changes in the joint that might have been revealed by a radiographic examination.

In addition, the small samples of stroke survivors and healthy controls that were used in these studies represent another limitation of this research. Finally, more than one training session may be required to enhance spatiotemporal symmetry by over 7-8% for step length and 16% for swing time in stroke survivors. However, it is not clear whether such a minor change in spatiotemporal symmetry would cause any obvious alteration to the joint load in question.

7.9 Conclusion

This thesis is the first work to characterise knee joint moments, both cross-sectionally and longitudinally, in chronic stroke survivors, after manipulating spatial and temporal walking asymmetry. While all frontal plane moments were found to be comparable to or lower than those of healthy subjects, walking at a similar speed, sagittal plane moments were higher on the non-paretic side. Left unchanged, heightened KFM increases the risk of knee joint pain

and OA. However, over time (two years), knee joint moment patterns were found to change, with joint moments on the frontal plane increasing and KFM decreasing. Knee joint moments did not manifest in notable changes as part of imposing symmetry on the stroke survivors. Furthermore, it is surprising that the stroke survivors with less spatiotemporal asymmetry displayed higher KFM than the healthy controls. These changes with time indicate the importance of considering how joint moments (as mechanical stimuli) change throughout the post-stroke lifespan, especially in light of the biological changes that usually accompany aging and increased BMI.

Joint moments were observed to be heavily influenced by compensatory gait patterns, such as pelvic tilt. This type of compensation, in addition to slow walking speed, may have the side-effect of helping to keep knee moment low on the frontal plane. Ultimately, this work highlights the need to consider the response of joint moments to rehabilitation and change over time. It explores the impact of post-stroke gait patterns on knee joint biomechanics, especially mechanical loading, by quantifying knee joint load. Moreover, it gives indications for future research and potential targets for gait rehabilitation to reduce the long-term risk of knee OA. However, future longitudinal work is necessary to investigate knee joint load from the very earliest stages of stroke recovery, taking into consideration cumulative load (physical activity), walking speed, and radiographic measurements of joint tissue.

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Appendices

Appendix A: Does Knee Joint Loading in Long-Term Stroke Recovery Indicate a Risk of Joint Degeneration? (chapter 4)

A.1. Between Labs difference (University of Salford vs. KFMC)

A.1.1 Aim

The aim of this experiment was to examine the repeatability of main outcome measures (Spatiotemporal, KAM and KFM) between two labs (Salford and KFMC).

A.1.2 Methods

This experiment involves one healthy participant who completed the data collection of 3D motion analysis system at two different gait labs: University of Salford, UK (Vicon system) and King Fahad Medical City(KFMC), Saudi Arabia (Qualisys system). The participant underwent the same testing procedures as described in the methods for the previous study (see Chapter 2, Section 2.4), as 7 days apart was the time between two occasions. Factors such as walking speed and foot wear were controlled across the measurement.

A.1.3 Result

Demographic data of the participant is presented in Table A.1. Participant spatiotemporal, KAM and KFM data of two labs were presented in Table A.2-A.3.

Table A. 1: Participant demographic data.

Participants Characteristics	
Gender	*Male*
Age (year)	39
Height (M)	1.7
Mass (kg)	81

Table A. 2: Mean and SD of the Spatiotemporal data between Salford and KFMC gait labs for the participant.

Spatiotemporal		Salford	KFMC
Walking speed (m/s)		1.31	1.26
Step Length (cm)	**Left**	0.71 (0.01)	0.71 (0.03)
	Right	0.69 (0.01)	0.67 (0.03)
Swing Time (s)	**Left**	0.41 (0.01)	0.44 (0.02)
	Right	0.41 (0.01)	0.42 (0.01)

Table A. 3: Mean and SD of the knee joint moments (Peak KAM, KAM impulse and peak KFM) data between Salford and KFMC gait labs for the participant.

Joint moments	Salford	KFMC
Peak KAM (Nm/Kg)	0.66 (0.09)	0.69 (0.08)
KAM Impulse(Nm/kg*s)	0.25 (0.04)	0.27(0.03)
Peak KFM (Nm/Kg)	0.55 (0.03)	0.52 (0.06)

A.1.4 Discussion and conclusion

The overall results of this experiment showed that there are minimal changes in spatiotemporal, KAM and KFM were between two labs. This is providing confidence that the biomechanical data which will be collected from individuals from the two labs will be within minimal error.

Appendix A.2: Ethical Approval

Research, Innovation and Academic Engagement Ethical Approval Panel

College of Health & Social Care
AD 101 Allerton Building
University of Salford
M6 6PU

T +44(0)161 295 2280
HSresearch@salford.ac.uk

www.salford.ac.uk/

2 March 2015

Dear Ulrike/Kris,

RE: ETHICS APPLICATION HSCR14-106: Speed accuracy trade-off in the control of footfall location during walking in stroke survivors

Based on the information you provided, I am pleased to inform you that your application has been approved.

If there are any changes to the project and/ or its methodology, please inform the Panel as soon as possible.

Yours sincerely,

Sarah Starkey

Sarah Starkey
Engagement & Innovation Assistant

Appendix A.3: Participant Information Sheet

Participant Information Sheet

Speed accuracy trade-off in the control of footfall location during walking in healthy young and older adults, and stroke survivors

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

Ask us if there is anything that is not clear or if you would like more information.

Take time to decide whether or not you wish to take part.

Why is this study being carried out?

This is a study to investigate how the control of foot-placement during walking is affected by a single session of training walking at different speeds. This is an important issue for the rehabilitation of older adults at risk of falling and stroke survivors. In general, humans make many more errors when moving faster. For example, reaching to a small target is much less accurate (has more error) if you must reach quickly. Similarly, it is much more difficult to step quickly to a safe foot-placement, as might be necessary when avoiding stepping on rocks (or dog doo!). This is especially problematic for older adults and/or stroke survivors who may be at risk of falling. In previous studies, we have seen that practicing to reach at different speeds may decrease the errors of reaching quickly. If the same result were found in the control of foot-placement during walking this could be important for the rehabilitation of walking. One of the key goals of rehabilitation of walking is to improve walking speed so that people are able to cross a street in the time allowed by traffic lights (among other things). But if walking faster is at the cost of more errors in foot-placement, causing stumbling or falling, then walking faster could be less safe. We are therefore studying if errors in the control of foot-placement during walking can be reduced by practicing walking at specific speeds.

Why have you been chosen?

Everyone in your community group who is more than 18 years old (for healthy adult participants) **OR** had a stroke more than 6 months ago and is able to walk 10 metres in 25 seconds (or less), safely, without any help from someone else or a walking aid, is being invited to participate.

Do you have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form, you are free to withdraw at any time without giving a reason and your participation in your normal community support groups, or the University of Salford will not be affected in anyway.

What will happen to me if I take part?

If you decide to take part, the researchers will arrange an appointment for you to attend the University of Salford at your convenience. **If you are a stroke survivor** who needs help arranging transportation, the researcher will help you do this and your **travel will be reimbursed**.

All participants will be asked to take part in the same measures and testing at **the University of Salford for a maximum of 4 hours in a single session**.

We will perform clinical physiotherapy assessments of your balance and general walking ability, including standing on a forceplate measuring the sway of your body in response to different visual scenes on a screen in front of you. These measures, that will take no more than 30mins, can be performed at the community group before you come to the University, which will ensure that the tests and walking training we will do at the laboratory is suited to your walking abilities.

In the laboratory, we will measure how you control your foot-placement while walking at different speeds on a treadmill. We will then ask you to practice walking to targets on the treadmill at a set speed (either faster or slower than your normal pace).

We will repeat the measures to assess your foot-placement at different speeds to see if this training has changed the way that you walk.

The walking measures and training involve walking on a treadmill (while wearing a safety harness) and stepping to foot-step targets that are shone (using an overhead projector) onto the floor of the treadmill. We will ask you to walk at your own comfortable speed and also 50% slower and faster than this comfortable speed. If you cannot walk 50% faster, we will ask you to walk as quickly as you can. We will perform these measures at the beginning and at the end of the session and testing will consist of a maximum of 360 steps.

During the training block we will ask you to only practice walking to the targets at a set speed (either fast or slow). The foot-step targets that are lit-up on the floor of the treadmill will vary in size and sometimes you will have to step to small targets and sometimes to large targets. There will be a maximum of 360 steps taken.

The whole session will therefore require 1080 steps (3 x 360). A longer rest will be taken between the testing and training and shorter breaks after every 60 steps. You can additionally take **rest breaks whenever you need them**.

We will ask you to wear trainers, shorts and a t-shirt to allow us to measure your walking using infra-red cameras that measure the movement of 18 small reflective markers which will be placed on your hips, thigh, calf, and foot using medical tape. These camera systems do not record images of you, they only measure the

movement of the reflective dots on your legs and hips and you cannot be identified from the images these cameras take.

How long will it take?

The three blocks (testing, training, testing) will each take less than an hour. But we ask that you allow a **maximum of 4hrs per visit** as we will need some additional time to welcome you to the University, to let you get familiar with the task of walking on the treadmill, to do the physiotherapy assessments of balance and to have rest breaks whenever you need them.

Only you and the researchers will be present during the testing sessions, though **you are welcome to have a friend, carer or family member stay with you if you wish.**

What are the possible disadvantages and risks of taking part?

This study is considered to be low risk in which we do not anticipate serious difficulties like falling or fatigue. Participation in the study requires only walking of very low intensity, with rests whenever necessary and while **wearing a safety harness**. If you stumble while walking on the treadmill the safety harness will catch you (so you will not reach the floor) and the treadmill will stop immediately.

However, should any difficulty occur, there will be 2 researchers present throughout the testing and training sessions to help you and a first aider is on call during testing. You are also welcome to bring along a friend/family member or carer if you wish.

What are the possible benefits of taking part?

You will not benefit directly from taking part in this research but the results of this study will help inform the design of rehabilitation programs for stroke survivors and frail elderly individuals.

What will happen if I do not want to carry on with the study?

You can withdraw from the study at any time without giving a reason. If you decide to withdraw, all information we have collected will be retained and used as part of the study, unless you request it to be deleted.

Will my taking part in this study be kept confidential?

Any information obtained in connection with this study will be treated as privileged and confidential. All information will be anonymous so that you cannot be identified by others and the paper base document will be stored securely in a locked cabinet at the University of Salford. Electronic data will be password protected. None of the camera recordings of the movement of the markers during walking record any images of you. The motion analysis system used records only the markers and so you are not identifiable from these recordings.

Contact details

If you have any questions or would like more information, please do not hesitate to contact:

Ulrike Hammerbeck
College of Health and Social Care
University of Salford
Allerton Building
Frederik Road campus
Salford M6 6PU
Email: u.hammerbeck@salford.ac.uk
Tel : 0161 295 2017

If you are unhappy with the study, please contact :

Dr. Kristen Hollands
College of Health and Social Care
University of Salford
Allerton Building
Frederik Road campus
Salford M6 6PU
Email: k.hollands@salford.ac.uk
Tel : 0161 295 3238

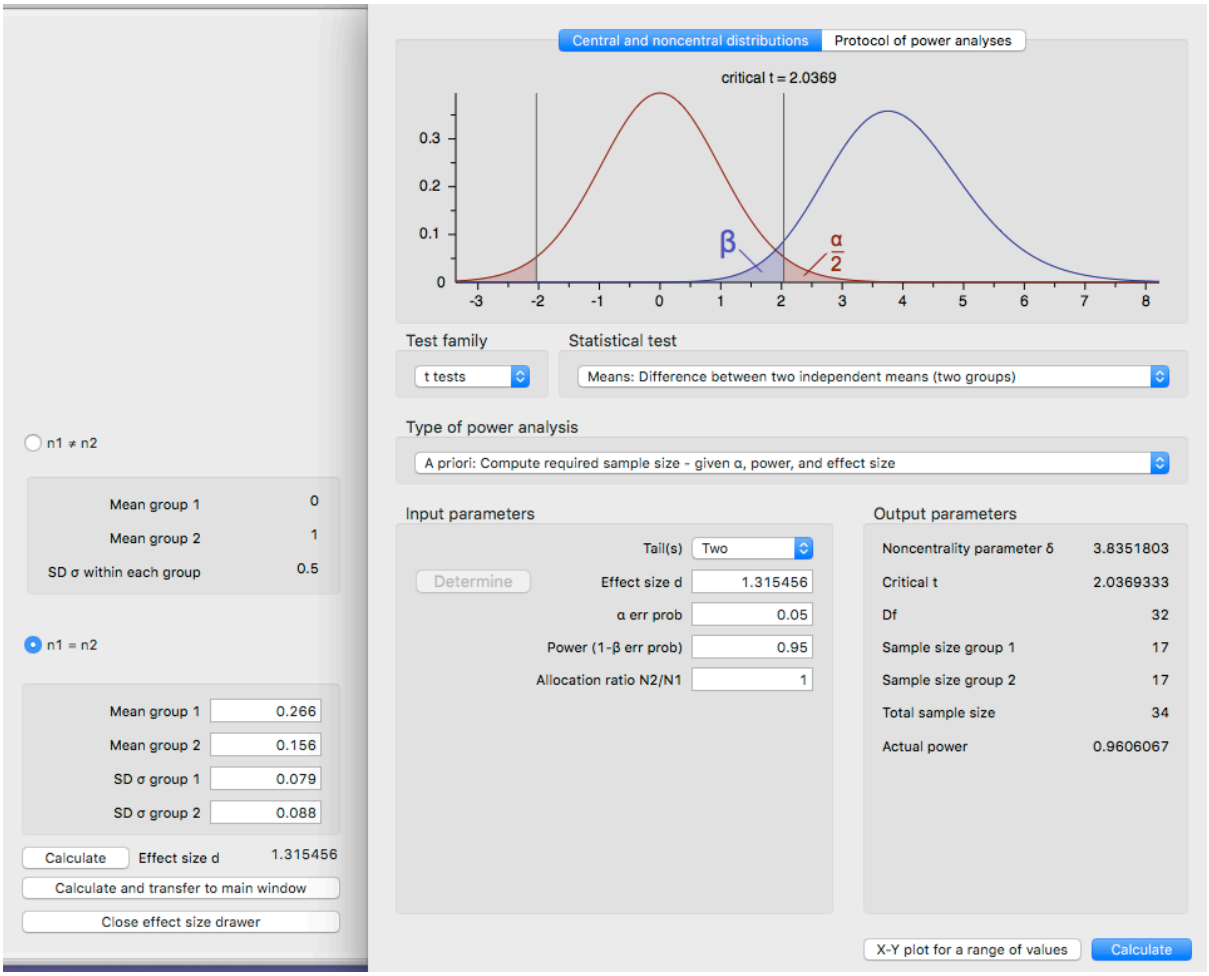
Thank you for taking time to read this information.

Appendix A.4: Comparison between healthy controls' right and left limbs (Paired t-test).

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	KAM_L_SS - KAM_R_SS	.02889	.07568	.01784	-.00875	.06653	1.619	17	.124
Pair 2	KAM_L_08 - KAM_R_08	.00889	.08130	.01916	-.03154	.04932	.464	17	.649
Pair 3	KAMImpulse_L_SS - KAMImpulse_R_SS	.00111	.03085	.00727	-.01423	.01645	.153	17	.880
Pair 4	KAMImpulse_L_08 - KAMImpulse_R_08	-.00278	.05399	.01273	-.02963	.02407	-.218	17	.830
Pair 5	KFM_L_SS - KFM_R_SS	-.00500	.16343	.03852	-.08627	.07627	-.130	17	.898
Pair 6	KFM_L_08 - KFM_R_08	-.02167	.10612	.02501	-.07444	.03111	-.866	17	.398

Appendix A.5: Sample size calculation



Appendix A.6: Normality tests

A.6.1: Stroke survivors (Cohort)

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
KAM_allStroke_P	.111	17	.200*	.954	17	.523
KAM_allStroke_NP	.164	17	.200*	.915	17	.121
KAMImpulse_allStroke_P	.182	17	.139	.904	17	.080
KAMimpulse_allStroke_NP	.163	17	.200*	.951	17	.466
KFM_allStroke_P	.118	17	.200*	.930	17	.215
KFM_allStroke_NP	.151	17	.200*	.915	17	.121

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

A.6.2: Healthy control

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
KAM_HealthySS	.165	18	.200*	.936	18	.246
KAM_Healthy08	.100	18	.200*	.972	18	.834
KAMImpulse_HealthySS	.209	18	.037	.901	18	.061
KAMImpulse_Healthy08	.126	18	.200*	.970	18	.802
KFM_HealthySS	.145	18	.200*	.937	18	.258
KFM_Healthy08	.152	18	.200*	.926	18	.164

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

A.6.3: Stroke survivors between visits (Longitudinal)

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
PKAM_P_V1	.140	9	.200*	.950	9	.691
PKAM_P_V2	.188	9	.200*	.910	9	.318
PKAM_NP_V1	.216	9	.200*	.940	9	.580
PKAM_NP_V2	.232	9	.178	.898	9	.238
KAM_IMP_P_V1	.178	9	.200*	.881	9	.160
KAM_IMP_P_V2	.182	9	.200*	.898	9	.242
KAM_IMP_NP_V1	.231	9	.183	.860	9	.096
KAM_IMP_NP_V2	.133	9	.200*	.966	9	.857
KFM_P_V1	.168	9	.200*	.933	9	.509
KFM_P_V2	.162	9	.200*	.898	9	.242
KFM_NP_V1	.166	9	.200*	.956	9	.757
KFM_NP_V2	.160	9	.200*	.897	9	.234

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

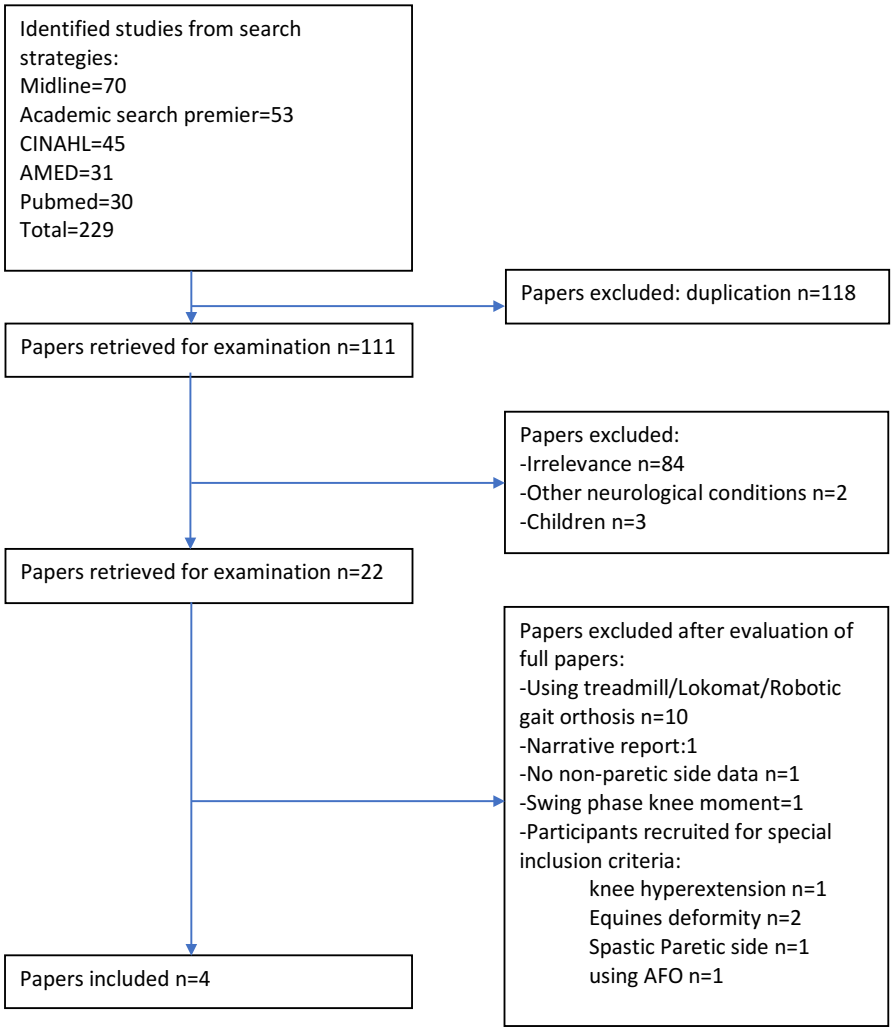
Appendix A.7: search strategies for stroke survivors' moment asymmetry

The following online databases (EBSCO) (Midline, Academic search premier, CINAHL), AMED (Ovid) and PubMed were searched.

The search strategy included a combination of three/four group of keywords as a follow:

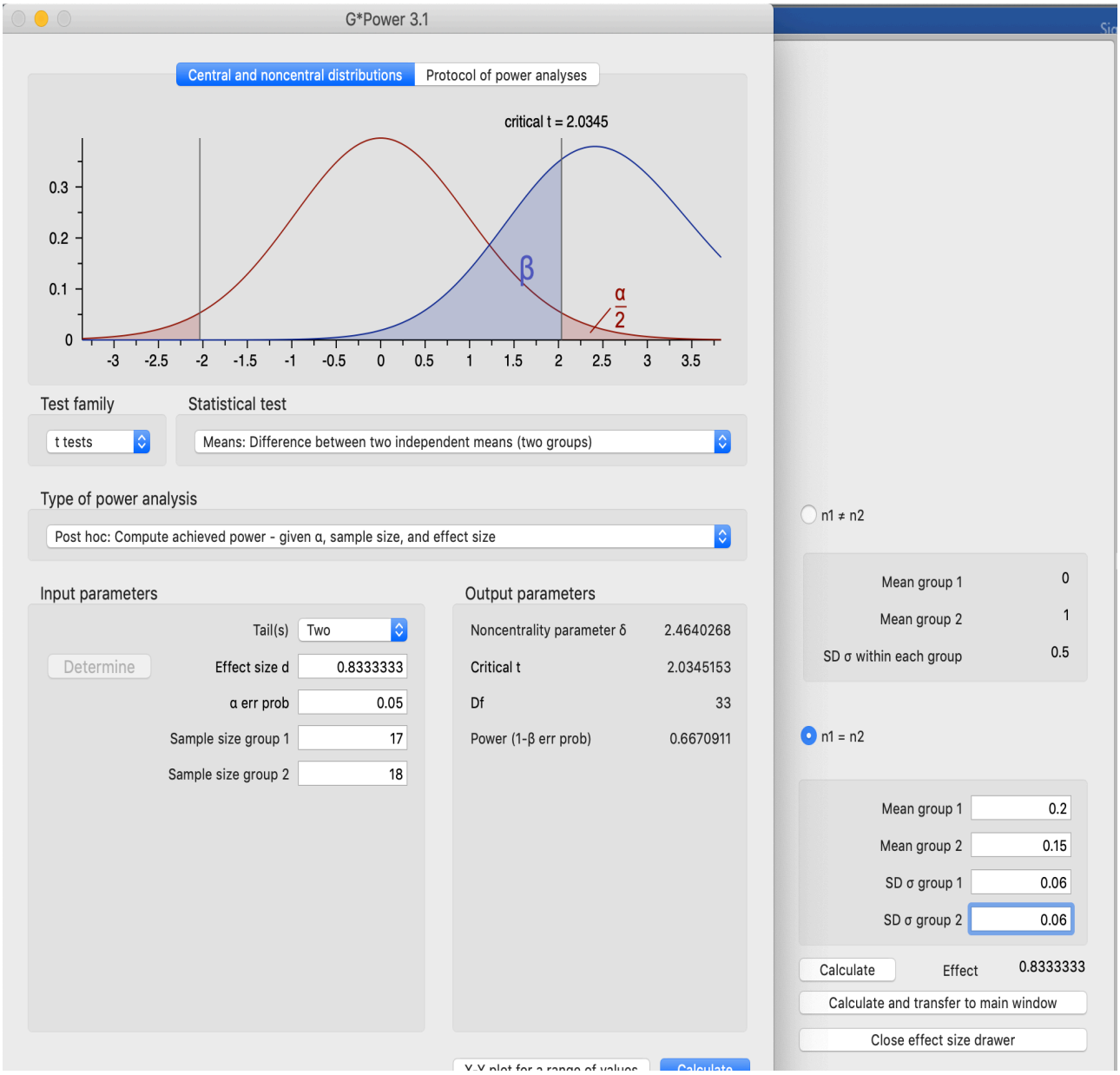
- Condition-related: stroke or hemiplegia* or cerebrovascular or CVA
- Functional-related: gait or walk*
- Joint-related: knee
- Outcome-related: moment or Kinetics

Limiter: Human and English.

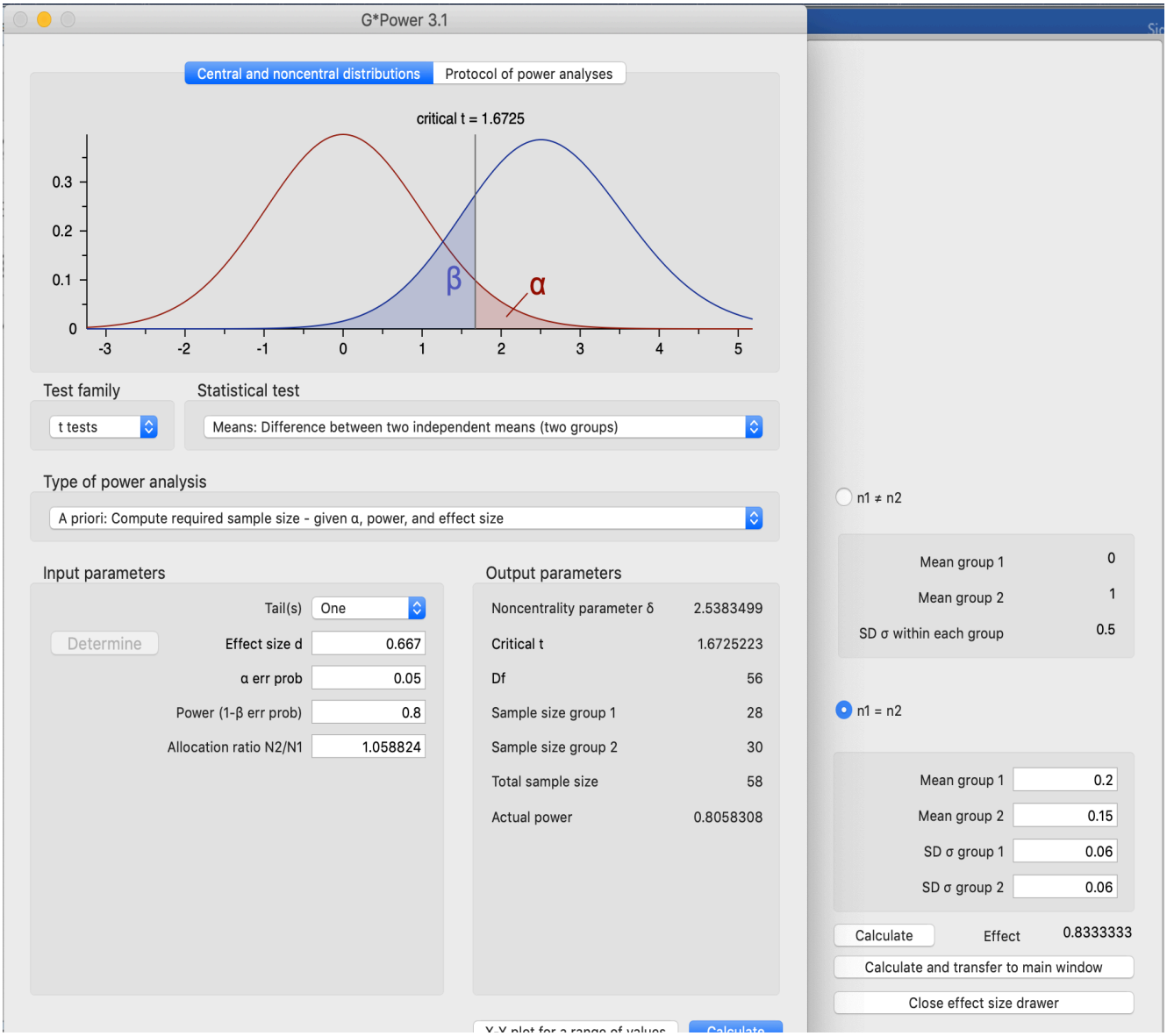


Appendix A.8: Post-hoc power analysis of cohort study

A.8.1: Post-hoc power analysis calculation



A.8.2: Sample size required- Based on Post-hoc power analysis.



Appendix B: The influence of Imposing temporal gait symmetry on knee joint kinetic profiles in individuals with stroke (Chapter 5)

Appendix B.1: Ethical Approval from University of Salford

Research, Innovation and Academic Engagement Ethical Approval Panel

Research Centres Support Team
G0.3 Joule House
University of Salford
M5 4WT

T +44(0)161 295 2280

www.salford.ac.uk/

20 January 2017

Dear Sultan,

RE: ETHICS APPLICATION–HSR1617-29 –'The influence of imposing temporal gait symmetry on knee joint kinetic profiles in individuals with stroke.'

Based on the information you provided I am pleased to inform you that application HSR1617-29 has been approved.

If there are any changes to the project and/or its methodology, then please inform the Panel as soon as possible by contacting Health-ResearchEthics@salford.ac.uk

Yours sincerely,

Sue McAndrew
Chair of the Research Ethics Panel

Appendix B.2: Ethical Approval from King Fahad Medical City

Kingdom of Saudi Arabia
Ministry of Health
King Fahad Medical City
(162)

وزارة الصحة
مدينة الملك فهد الطبية
King Fahad Medical City

المملكة العربية السعودية
وزارة الصحة
مدينة الملك فهد الطبية
(١٦٢)

IRB Registration Number with KACST, KSA: H-01-R-012
IRB Registration Number with OHRP/NIH, USA: IRB00010471
Approval Number Federal Wide Assurance NIH, USA: FWA00018774

July 18, 2016
IRB Log Number: 16-243
Department: Rehabilitation Hospital
Category of Approval: EXPEDITED

Dear Mr. Sultan Al Harbi,

I am pleased to inform you that submission dated July 4, 2016 for the study titled '**The influence of inducing temporal gait symmetry on knee joint kinetic profiles in individuals with stroke**' was reviewed and was approved according to Good Clinical Practice guidelines.

Please be informed that in conducting this study, you as the Principal Investigator are required to abide by the rules and regulations of the Government of Saudi Arabia, the KFMC/IRB policies and procedures, and the ICH Good Clinical Practice guidelines. Further, you are required to submit a Progress Report before June 18, 2017; it can be reviewed by the IRB without lapse of approval. The approval of this proposal will automatically be suspended on July 18, 2017 pending the acceptance of the Progress Report. You also need to notify the IRB as soon as possible in the case of:

1. Any amendments to the project;
2. Termination of the study;
3. Any serious unexpected adverse events (within two working days);
4. Any event or new information that may affect the benefit/risk ratio of the proposal.

Please observe the following:

1. Personal identifying data should only be collected when necessary for research;
2. The data collected should only be used for this proposal;
3. Data should be stored securely so that a few authorized users are permitted access to the database;
4. Secondary disclosure of personal identifiable data is not allowed;
5. Copy of the Consent Form should be kept in the Research Subject's Medical Record and the consent process should be documented in the medical record;
6. Copy of the pharmacy clearance (IDS) must be in the medical record.

Please be advised that regulations require that you submit a progress report on your research every 6 months. You are also required to submit any manuscript resulting from this research for approval by IRB before submission to journals for publication.

Appendix B.3: Participant Information Sheet

University of Salford MANCHESTER

Participant Information sheet

The influence of Imposing temporal gait symmetry on knee joint kinetic profiles in individuals with stroke

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

Ask us if there is anything that is not clear or if you would like more information.
Take time to decide whether or not you wish to take part.

Why is this study being carried out?

Improving asymmetry of walking (e.g. making step lengths equal on each leg) in stroke survivors is very important because it improves the appearance of walking and reduces the effort of walking thus improving participation. However, we do not know the impact of imposing gait symmetry on the forces at joints. Therefore, the aim of this study is to explore the immediate effect of imposing gait symmetry on joint forces (increase or decrease joint load) in stroke survivors and healthy older adults.

Why are we inviting you to take part?

Everyone in your community group who is more than 18 years old (for healthy adult participants) **OR** had a first stroke (any time since the onset), has been referred for gait rehabilitation and is able to walk 10 metres in 25 seconds (or less), safely, without any help from someone else or a walking aid, is being invited to participate.

Do you have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form, you are free to withdraw at any time without giving a reason and your participation in your normal community support groups, or the University of Salford will not be affected in anyway.

What will happen to me if I take part?

If you decide to take part, the researchers will arrange an appointment for you to attend the University of Salford at your convenience. **If you are a stroke survivor** who needs help arranging transportation like taxi, the researcher will help you to do this by ordering it in advance for the agreed time of participation. If you are traveling to us, then your **travel expenses will be reimbursed** directly to your bank account at the time of visiting the lab to take part. To do this, you should bring along a receipt for the travel expenses (e.g. train ticket etc.) and fill in and sign a form for reimbursement.
All participants will be asked to take part in the same measures and testing at the gait laboratory at Brian Blatchford building, University of Salford, **for a <u>maximum</u> of four hours in a single session**.

We will perform clinical physiotherapy assessments of your balance and general walking ability. These measures, that will take no more than 30mins, can be performed at the beginning of your visit to the gait lab. This will help ensure that the walking we will do is suited to your walking abilities.
In the laboratory, we will measure your walking in three different conditions, at your own speed, with 5 attempts at each condition. **For stroke survivors, we will measure your walking when you**:

1) Walk normally (no metronomes or stickers to step on),
2) Walk while stepping on footstep targets which will make your step lengths equal on both sides and
3) Walk while timing your steps to the beat of a metronome which will make the timing of your steps equal on both sides.

For healthy adults, we will also measure your walking in the 3 different conditions above with 5 attempts at each condition. However, the footstep targets will be spaced on the floor so that you walk asymmetrically (uneven step lengths on each side or uneven time between steps on each side). We will also ask healthy aged-match participants to walk in each of the three conditions at self-selected walking speed as well as two different slow speeds (0.4 m/s and 0.8 m/s) to match stroke participants walking speed.

We will ask you to wear comfortable trainers, shorts and a t-shirt to allow us to measure your walking using infra-red cameras that measure the movement of 18 small reflective markers which will be placed on your hips, thigh, calf, and foot using medical tape. These camera systems do not record images of you, they only measure the movement of the reflective dots on your legs and hips and you cannot be identified from the images these cameras take.

How long will it take?

The single testing session will take less than 3 hours. But we ask that you allow a **maximum of 4 hrs** as we will need some additional time to welcome you to the University, to let you get familiar with the task of different walking conditions, to do the physiotherapy assessments of balance and to have rest breaks whenever you need them.

Only you and the researchers will be present during the testing sessions, though **you are welcome to have a friend, carer or family member stay with you if you wish.**

What are the possible disadvantages and risks of taking part?

This study is considered to be low risk in which we do not anticipate serious difficulties like falling or fatigue. Participation in the study requires only walking of very low intensity, with rests whenever necessary.
However, should any difficulty occur, there will be 2 researchers present throughout the testing and training sessions to help you and a first aider is on call during testing. You are also welcome to bring along a friend/family member or carer if you wish.

What are the possible benefits of taking part?

You will not benefit directly from taking part in this research but the results of this study will help inform the design of rehabilitation programs for stroke survivors and frail elderly individuals.

What will happen if I do not want to carry on with the study?

You can withdraw from the study at any time without giving a reason. If you decide to withdraw, all information we have collected will be retained and used as part of the study, unless you request it to be deleted.

Will my taking part in this study be kept confidential?

Any information obtained in connection with this study will be treated as privileged and confidential. All information will be anonymous so that you cannot be identified by others and the paper base document will be stored securely in a locked cabinet at the University of Salford. Electronic data will be password protected. None of the camera recordings of the movement of the markers during walking record any images of you. The motion analysis system used records only the markers and so you are not identifiable from these recordings.

Further information and contact details:

If you have any questions or would like more information, please do not hesitate to contact:

Mr. Sultan Alharbi
College of Health and Social Care
University of Salford
Allerton Building
Frederik Road campus
Salford M6 6PU
Email: s.Alharbi@edu.salford.ac.uk
Tel : 07476985384

If you are unhappy with the study, please contact :

Dr. Kristen Hollands
College of Health and Social Care
University of Salford
Allerton Building
Frederik Road campus
Salford M6 6PU
Email: k.hollands@salford.ac.uk

Thank you for taking time to read this information.

Appendix B.4: Healthy participants from the spatial symmetrical sub-group who were considered separately

Table B.4-1: Supplementary data for the three healthy participants who were considered separately because of non-exceeding the target step length asymmetry ratio of 1.08 (the upper step length symmetry ratio limit of healthy).

	Participant id	SPEEDS	1MC09	1MM13	KFMC01	Mean	SD
Demographic Data	Gender		M	M	M		
	Age (y)		61	52	36	49.67	12.66
	Height (m)		1.78	1.71	1.77	1.75	0.04
	Weight (kg)		78	75	68	73.67	5.13
	Affected leg		L	L	R		
	Time since stroke (month)		43.00	21	25	29.67	11.72
	Berg Balance (out of 56)		45.00	52	54	50.33	4.73
	TUG		17.39	19.38	10.15	15.64	4.86
	KOOS		100	100.00	100.00	100.00	0.00
	10 m -walk (m/s)		0.67	0.51	1.14	0.77	0.33
	Fugl-Meyer_lower_limb (out of 34)		28.00	18	30	25.33	6.43
	Fugl-Meyer_sensory		10.00	12	12	11.33	1.15
	3D sys. Walking speed 6m (m/s)	Baseline	0.73	0.54	1.18	0.82	0.33
		Spatial	0.71	0.52	0.99	0.74	0.24
Spatiotemporal	**Slen_(Paretic)**	Baseline	0.52	0.51	0.63	0.55	0.07
		Spatial	0.53	0.53	0.56	0.54	0.02
	Slen_(Non-Paretic)	Baseline	0.5	0.52	0.61	0.54	0.06
		Spatial	0.51	0.54	0.57	0.54	0.03
	Slen_ratio	Baseline	1.04	1.02	1.03	1.03	0.01
		Spatial	1.04	1.02	1.02	1.03	0.01
Moment	Peak EKAM 0-50 Stance (Paretic)	Baseline	0.19	0.54	0.69	0.47	0.26
		Spatial	0.2	0.51	0.59	0.43	0.21
	Peak EKAM 0-50 Stance (Non-Paretic)	Baseline	0.45	0.18	0.73	0.45	0.28
		Spatial	0.47	0.21	0.69	0.46	0.24
	EKAM_Impulse (Paretic)	Baseline	0.11	0.29	0.17	0.19	0.09
		Spatial	0.12	0.27	0.17	0.19	0.08
	EKAM_Impulse (Non-Paretic)	Baseline	0.16	0.17	0.25	0.19	0.05
		Spatial	0.23	0.22	0.23	0.23	0.01
	Knee Flex Moment (Paretic)	Baseline	0.62	0.02	0.52	0.39	0.32
		Spatial	0.69	0.03	0.49	0.40	0.34
	Knee Flex Moment (Non-Paretic)	Baseline	0.65	0.2	1.34	0.73	0.57
		Spatial	0.47	0.24	1.27	0.66	0.54
						#DIV/0!	#DIV/0!